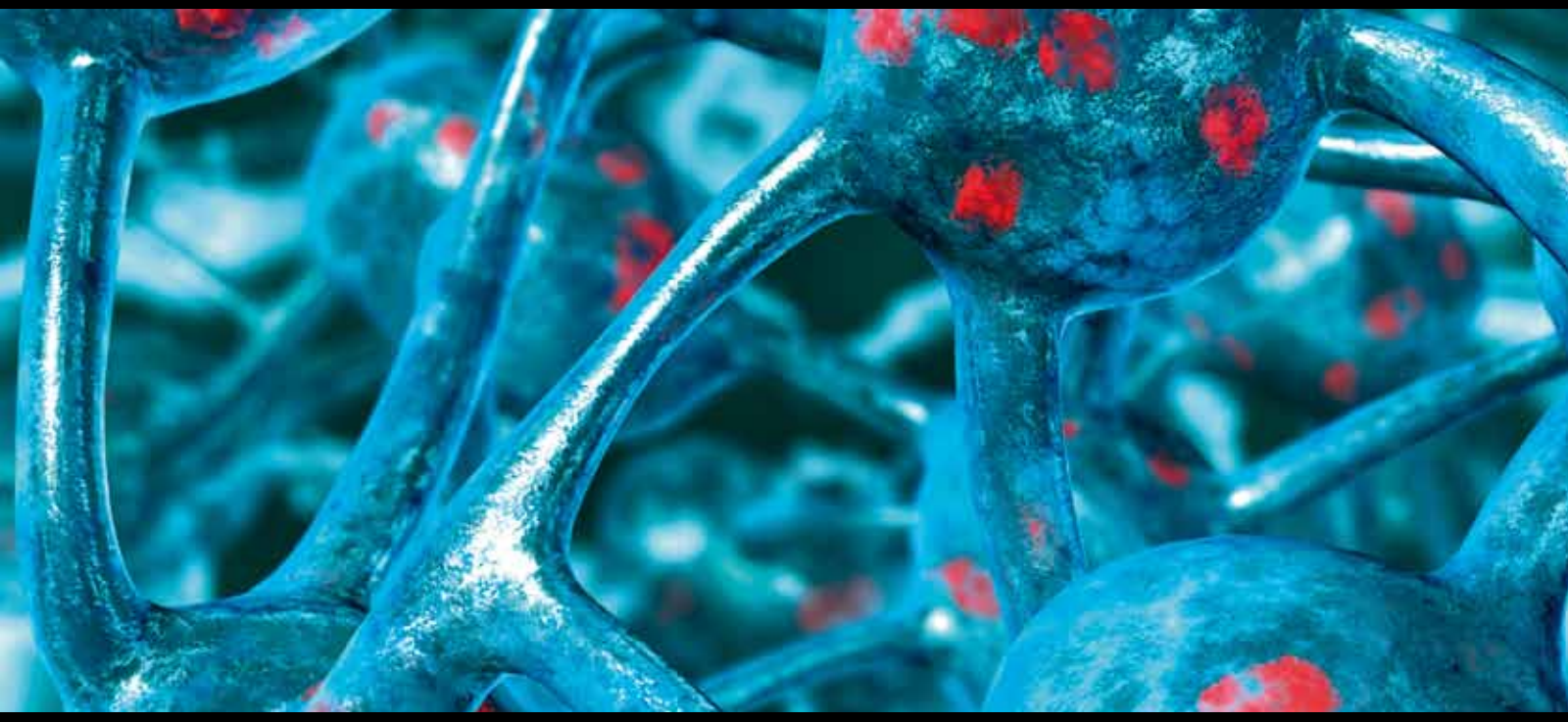
Neuropsychiatry of Parkinson's Disease

Guest Editors: Antonio L. Teixeira, Leonardo F. Fontenelle, Edward C. Lauterbach, and Sergio Starkstein



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Editorial Board

Contents

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Editorial

Neuropsychiatry of Parkinson's Disease

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Parkinson's disease (PD) is traditionally regarded as a motor or a movement disorder. In recent years, however, an increased interest has been directed to its nonmotor symptoms as they seem to determine significant disability at all stages of the disease. Some PD patients consider their nonmotor symptoms even more disabling than motor signs. Among these nonmotor symptoms, neuropsychiatric syndromes (or behavioral and psychological symptoms) are of paramount importance. They include a wide array of syndromes such as anxiety, depression, psychosis, impulse control disorders, apathy, and cognitive dysfunction. Their pathogenesis in PD is rather complex, involving neurodegenerative, drug-related, and psychological mechanisms. Their recognition and management represent a great challenge.

The paper by R. de la Fuente-Fernández presents a staging model named PD-related frontostriatal cognitive dysfunction (PDFCD) that provides a clinical and hypothesis-testing framework for neuropsychiatric syndromes in PD. De La Fuente-Fernandez's PDFCD model proposes three stages based on the sequential process of dopamine depletion occurring in different regions of the striatum (stages I and II) and the frontal cortex (stage III). Therefore, PD patients would present executive dysfunction and mental fatigue (stage I), depression/anxiety (stage IIa), apathy/pain (stage IIb), and dementia (stage III).

The paper by J. Calleo et al. summarizes the current literature on the cognitive rehabilitation programs in PD patients. Despite limited available data and heterogeneity of motor and nonmotor symptoms in PD, cognitive rehabilitation seems to be promising in this context.

The paper by Y. Bogdanova and A. Cronin-Golomb1 presents an original study that assessed cognitive correlates of anxiety and apathy in PD patients. In comparison with matched controls, PD patients exhibited higher levels of anxiety and apathy which were correlated with disease duration. Interestingly, anxiety and apathy correlated differently with cognitive functions. The question remains open whether the treatment of both conditions impacts on cognitive functioning in PD.

Until recently, most studies have focused on the impact of motor disability and depressive symptoms on the quality of life of PD patients, neglecting the role of anxiety. The paper by K. K. Hanna and A. Cronin-Golomb addressed this issue, reporting that anxiety, more than depressive, cognitive, and motor symptoms, significantly affected quality of life in PD.

Dopaminergic strategies remain the mainstay of PD treatment. However, they are frequently associated with neuropsychiatric syndromes, notably psychosis. Alternative therapeutic options have been searched in the last years, and adenosine A_{2A} receptor antagonists seem to be very promising. The paper by C. J. Bleickardt et al. demonstrates that, in comparison with dopamine receptor agonists, adenosine A_{2A} antagonists exhibit better neuropsychiatric profiles as they do not interfere with prepulse inhibition in rodents (a model of psychosis).

The paper by E. C. Lauterbach et al. presents a comprehensive review of the neuroprotective effects of the psychotropic drugs used in PD.

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Review Article

The Neuroprotective Disease-Modifying Potential of Psychotropics in Parkinson's Disease

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Neuroprotective treatments in Parkinson's disease (PD) have remained elusive. Psychotropics are commonly prescribed in PD without regard to their pathobiological effects. The authors investigated the effects of psychotropics on pathobiological proteins, proteasomal activity, mitochondrial functions, apoptosis, neuroinflammation, trophic factors, stem cells, and neurogenesis. Only findings replicated in at least 2 studies were considered for these actions. Additionally, PD-related gene transcription, animal model, and human neuroprotective clinical trial data were reviewed. Results indicate that, from a PD pathobiology perspective, the safest drugs (i.e., drugs least likely to promote cellular neurodegenerative mechanisms balanced against their likelihood of promoting neuroprotective mechanisms) include pramipexole, valproate, lithium, desipramine, escitalopram, and dextromethorphan. Fluoxetine favorably affects transcription of multiple genes (e.g., MAPT, GBA, CCDC62, HIP1R), although it and desipramine reduced MPTP mouse survival. Haloperidol is best avoided. The most promising neuroprotective investigative priorities will involve disease-modifying trials of the safest agents alone or in combination to capture salutary effects on H3 histone deacetylase, gene transcription, glycogen synthase kinase-3, α-synuclein, reactive oxygen species (ROS), reactive nitrogen species (RNS), apoptosis, inflammation, and trophic factors including GDNF and BDNF.

1. Introduction

Parkinson's disease (PD) and other neurodegenerative diseases are common and impose substantial morbidities and costs on patients, caregivers, and society [1–3]. Neuropsychiatric conditions occur in most patients with Parkinson's disease (PD), with 61–88% of patients reporting at least one psychiatric symptom [2]. Neuropsychiatric disorders include a variety of cognitive concerns, delirium, dementia, depression, anxiety, panic, and other conditions related either to PD itself or its treatment [2]. These neuropsychiatric morbidities are quite significant, with cognitive impairment and depression constituting two of the strongest determinants of PD quality of life [2]. As such, these conditions necessitate treatment.

Psychotropics are commonly used to treat these PD comorbidities without regard to their potential pathobiological effects [3, 4]. Furthermore, psychotropics are used in treating the dementias that attend PD (Parkinson's disease dementia, dementia with Lewy bodies, and Alzheimer's disease), eventually present in nearly all patients [1, 2]. Additionally, dopaminergic therapies (levodopa, dopamine agonists) and deep brain stimulation are associated with treatment complications including mania, gambling, hypersexuality, other impulse control disorders, and suicide attempts [2]. Psychotropics are widely prescribed for these conditions, again without considering their potential disease-modifying effects.

Psychotropics can directly [3] and indirectly [4] affect neurodegenerative pathobiology in a variety of ways [3, 4].

For example, a drug can directly affect apoptotic mechanisms and/or can indirectly affect apoptosis by its direct effects on pathogenic proteins, the proteasome, mitochondria, free radical formation, microglial activation, or inflammation [4]. Previous work had considered the effects of psychotropics on *intracellular* processes including proteins, proteasome, mitochondrion, and apoptosis [3], supplemented by a wider array of *extracellular* actions including neuroinflammation, trophic factors, neural and glial stem cells, and neurogenesis [4] across various cell types and models [3, 4]. The potential to modify the course of a neurodegenerative disease through these effects holds substantial implications for both PD patients and society as a whole [3, 5]. Figures 1 and 2 depict the relations and interrelations of these pathobiological mechanisms in regard to the viability of dopamine neurons.

Psychotropics may also affect the transcription of genes relevant to PD. The authors were therefore interested in exploring the effects of psychotropic drugs on each of these intracellular domains in published medical literature and gene expression databases. In this paper, we provide an update focusing on neuronal neurodegenerative mechanism findings that have been replicated in mature neural tissues or demonstrated in disease-relevant animal models. Second, a survey of psychotropic effects on the mRNA expression of genes relevant to PD risk and pathobiology was undertaken. Since genetic studies have revealed genes associated with PD risk and certain mutations are associated with various PD phenotypes, the ability of psychotropics to affect gene expression could potentially modify the course of PD with either deleterious or therapeutic potential. Third and finally, we consider the extant clinical trial literature as it pertains to first-line psychotropics and neuroprotection in PD.

2. Materials and Methods

2.1. Gene Expression Search. We comprehensively surveyed gene expression as a function of psychotropic treatment for genes associated with PD risk [6] and the classical PARK1-13 mutations associated with PD [7] and PARK14–16 by assessing literature in the PubMed (http://www.ncbi.nlm.nih.gov/pubmed) and Gene Expression Omnibus Profiles (GEO Profiles http://www.ncbi.nlm.nih.gov/sites/entrez?db=geo) databases. Risk-associated genes consisted of the genes most strongly associated with PD according to the PDGene database [6]. These genes were SNCA, MAPT/STH, NUCKS1, PM20D1, SLC41A1, BST1, LRRK2, USP24, SLC6A3, GBA, SLC45A3, SOD2, MTHFR, PLEKHM1, DGKQ, BDNF, PDXK, GWA 7p14.2, APOE, DRD3, GWA 2q36.3, GSTM1, PINK1, FGF20, CYP2D6, PARK2 (parkin), HLA-DRA, GLIS1, MAOB, CALB1, FARP1, LRP8, DRD2, UCHL1, GAK, MCCC1/LAMP3, STK39, SYT11, HLA-DRB5, CCDC62/HIP1R, ACMSD, and MED13. PARK 1–16 genes were also surveyed.

Drugs considered included first-line direct-acting D2/D3 dopamine agonists, antipsychotics, mood stabilizers, antidepressants, anxiolytics, and dextromethorphan combined with quinidine. While a primary treatment for the underlying disease, D2/D3 dopamine agonists are also used to treat apathy and have antidepressant qualities and were therefore included in this paper. Drugs were searched by their psychopharmacological category and by their specific names in each database. Specific drug search terms used were "neuroleptic OR atypical antipsychotic OR antipsychotic OR anxiolytic OR benzodiazepine OR antidepressant OR tricyclic antidepressant OR heterocyclic antidepressant OR SSRI OR selective serotonin reuptake inhibitor OR pramipexole OR ropinirole OR amantadine OR haloperidol OR fluphenazine OR trifluoperazine OR thiothixene OR chlorpromazine OR thioridazine OR risperidone OR olanzapine OR quetiapine OR ziprasidone OR aripiprazole OR clozapine OR paliperidone OR iloperidone OR asenapine OR tetrabenazine OR pimavanserin OR lithium OR carbamazepine OR oxcarbazepine OR valproate OR lamotrigine OR amitriptyline OR imipramine OR nortriptyline OR desipramine OR clomipramine OR trimipramine OR doxepin OR protriptyline OR maprotiline OR bupropion OR fluoxetine OR sertraline OR fluvoxamine OR paroxetine OR citalopram OR s-citalopram OR trazodone OR nefazodone OR venlafaxine OR duloxetine OR mirtazapine OR atomoxetine OR buspirone OR diazepam OR chlordiazepoxide OR flurazepam OR temazepam OR clorazepate OR clonazepam OR lorazepam OR oxazepam OR alprazolam OR zaleplon OR zolpidem OR zopiclone OR s-zopiclone OR cyproheptadine OR hydroxyzine OR diphenhydramine OR benztropine OR trihexyphenidyl OR modafinil OR ramelteon OR dextromethorphan OR quinidine." Levodopa was not reviewed because it generally is not prescribed to treat behavioral problems. Cognitive enhancers (cholinesterase inhibitors and NMDA antagonists) are not reviewed here because they have an extensive literature that has been reviewed elsewhere. The term "AND (mRNA OR gene expression)" was added to gene names, symbols, aliases, and drug terms in PubMed. A variety of models and treatment durations were encountered. Because psychotropics tend to be administered chronically in the clinical treatment of PD, only reports of chronic administration (at least 3-week duration in animal studies) are considered here.

Gene expression data in GEO Profiles was considered if a given treatment was compared to untreated controls under the same experimental conditions and if the data involved at least 2 determinations at a single locus (solitary determinations can be unreliable). Gene expression data in GEO Profiles were found for the selective serotonin reuptake inhibitor (SSRI) antidepressant fluoxetine, the neuroleptic antipsychotic haloperidol, and the atypical antipsychotics olanzapine and clozapine. Fluoxetine was administered for 21 days in mice, and gene expression was determined relative to untreated controls in the hippocampus (GEO Profiles accession number GDS2803) using the Affymetrix Gene Chip^R Mouse Genome 430 2.0 Array [8]. Olanzapine was given for 21 days in rats, and gene expression was compared to untreated controls in the frontal cortex (accession number GDS2608) using the Affymetrix Gene Chip^R Rat Genome 230 2.0 Array [9]. Results for haloperidol and clozapine relative to untreated control mice reflect gene expression in brain after treatment for 4 weeks (accession number GDS2537) using the Affymetrix Gene Chip^R Murine Genome U74

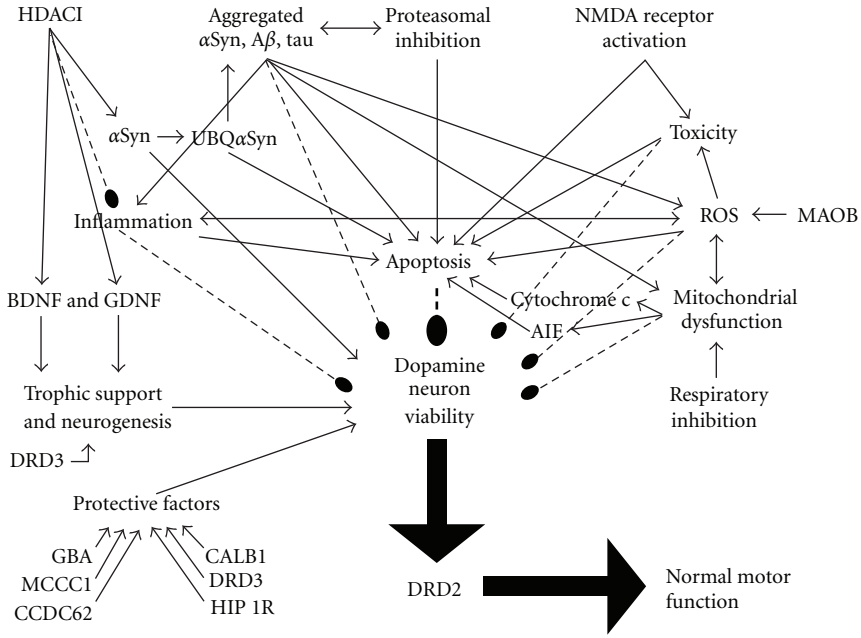

Figure 1: Factors affecting the viability of dopamine neurons. Relations terminating in an arrowhead indicate facilitation, those with double arrowheads indicate mutual facilitation, and dashed lines terminating in a bulb indicate inhibition. Though still being settled, recent data suggest that alpha-synuclein (αSyn) is neuroprotective whereas monoubiquitylated αSyn, aggregated αSyn, and other pathogenic proteins promote neurodegeneration. H3 histone deacetylase inhibition (HDACI) increases αSyn, brain derived neurotrophic factor (BDNF), and glial derived neurotrophic factor (GDNF), supporting neuronal synapses (αSyn) and providing trophic support for neurons and promoting neurogenesis (BDNF and GDNF). Neurotrophism appears to be facilitated by D3 dopamine receptor stimulation. HDACI also inhibits inflammation. Aggregated proteins inhibit the proteasome, promote reactive oxygen species (ROS), mitochondrial dysfunction, inflammation, and apoptosis, and impair neuronal viability. Inhibition of the proteasome results in reduced elimination of obsolete proteins, increases in aggregated protein species, facilitates apoptosis, and impairs neuronal viability. N-methyl-D-aspartate (NMDA) receptor activation by glutamate promotes neurotoxicity and apoptosis. Generation of peroxide radicals by MAOB promotes ROS. ROS and inflammation mutually promote each other, and each can induce apoptosis. Mitochondrial dysfunction and ROS also mutually promote each other. Impaired mitochondrial respiration through inhibition of respiratory chain complexes (I-IV) can produce mitochondrial dysfunction. Mitochondrial dysfunction leads to the loss of the mitochondrial membrane potential, opening of the mitochondrial permeability transition pore, and the release of cytochrome c and apoptosis inhibiting factor (AIF). Cytochrome c and AIF each independently trigger apoptosis. Protective factors against neurodegeneration include GBA, DRD3, CALB1, and other gene products. Thus, neurodegenerative processes include pathogenic proteins, proteasomal dysfunction, glutamate and other toxic molecules, NMDA receptor activation, ROS, mitochondrial dysfunction, apoptotic pathway activation, and subsequent neuroinflammation, in turn potentially inducing further ROS and apoptosis. Neuroprotective factors include GBA, MCCC1, CCDC62, HIP1R, DRD3, CALB1, αSyn, HDACI, BDNF, and GDNF. Neuroprotective factors promote while neurodegenerative processes impair the viability of the dopamine neuron. Nigral dopamine neurons promote normal motor functioning by release of dopamine on striatal D2 receptors, transcribed from the DRD2 gene, and reduced D2 stimulation is associated with Parkinson motor features.

Version 2 Array [MG_U74Av2] and 12 weeks (accession number GDS2531) using the Affymetrix Gene Chip^R Mouse Expression 430A Array [MOE430A]. Investigations were limited to murine species in GEO Profiles, and no studies of gene expression in the substantia nigra or striatum were encountered.

Reporting of GEO Profiles findings is limited to genes where specific probe sets were upregulated or downregulated by at least 20%. Percentage change for a given reporter probe set was calculated as the difference of the reporter probe value for treated animals from its untreated control values divided by that control value. In cases where there were positive findings for any gene probe set, probe sets were assessed to determine their reliability in assaying gene expression. Results are provided for genes for which changes in expression were observed after considering probe set reliability. Normalized expression data in GEO Profiles were derived from a gene chip and remain to be confirmed by quantitative real-time polymerized chain reaction (RT-PCR) or other analyses.

2.2. Posttranscriptional Neurodegenerative Mechanisms Search. Relevant studies were identified through a literature search of *intracellular* and *extracellular* neurodegenerative mechanisms (PubMed search terms: (alpha-synuclein OR beta-amyloid OR tau OR TDP-43 OR ubiquitin OR proteasome OR mitochondrial viability OR mitochondria OR mitochondrial transition pore OR cytochrome c release OR endosome OR lysosome OR autophagy OR endoplasmic reticulum OR leukocyte viability OR apoptosis OR inflammation OR trophins OR neurogenesis OR BDNF OR GDNF OR neural stem cells) AND (neuron OR neuronal OR

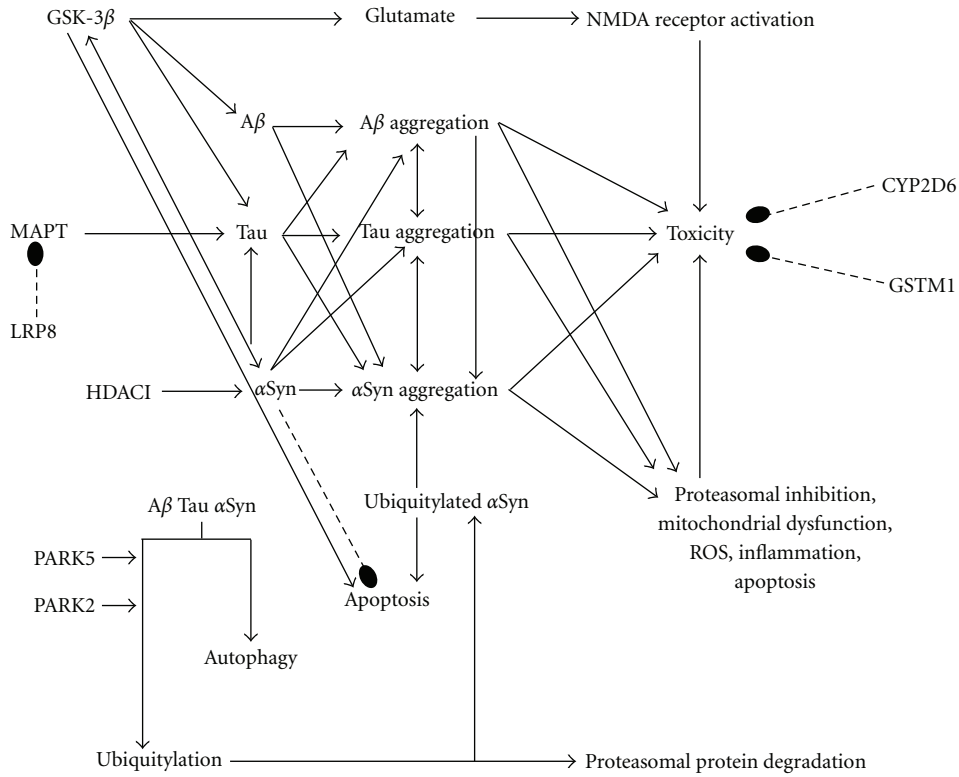

Figure 2: Interactions of neuroprotective and neurodegenerative pathways emphasizing pathogenic proteins and toxins. Relations terminating in an arrowhead indicate facilitation, those with double arrowheads indicate mutual facilitation, whereas dashed lines terminating in a bulb indicate inhibition. The enzyme glycogen synthase kinase 3 beta (GSK-3β) activates glutamatergic excitotoxicity mediated through the N-methyl-D-aspartate (NMDA) receptor. GSK-3β also drives production of alpha-synuclein (αSyn), the pathogenic proteins beta-amyloid (Aβ) and tau, and apoptosis. Whereas αSyn appears to be neuroprotective and inhibits apoptosis, mono-ubiquitylated αSyn promotes αSyn aggregation and apoptosis. On the other hand, αSyn can also increase GSK-3β and tau concentrations, in turn increasing aggregated αSyn, Aβ, and tau itself. Tau can further increase concentrations of αSyn. Aggregated αSyn, Aβ, and tau inhibit the proteasome and induce cellular toxicity, reactive oxygen species (ROS), mitochondrial dysfunction, apoptosis, and inflammation, leading to neuronal demise. The three proteins promote the formation of each other, as do their aggregated forms. The LRP8 gene product stabilizes microtubule associated protein tau (MAPT), the gene that produces tau protein, and dysfunctional LRP8 leads to excessive MAPT expression, increasing tau and driving pathogenic protein aggregation. Pathogenic proteins are disposed of through autophagy and the ubiquitin-proteasomal system, wherein proteins targeted for destruction are polyubiquitylated, a process that appears to be regulated by PARK5 (UCHL1) and PARK2 (parkin). Interference with autophagy or ubiquitylation prevents disposal of proteins, leading to their accumulation and their subsequent inhibition of the proteasome. GSTM1 and CYP2D6 gene products promote solvent detoxification, and deficiencies in these proteins permit toxicity. GSTM1 is particularly important in the context of CYP2D6 dysfunction.

neurons OR glia OR glial OR neuroglia)). These terms were joined by the operator "AND" to the drug search terms detailed in the gene expression section, except that only the specific drugs listed were searched (the pharmacological class search terms were omitted, specifically "neuroleptic OR atypical antipsychotic OR antipsychotic OR antidepressant OR anxiolytic OR benzodiazepine OR antidepressant OR tricyclic antidepressant OR heterocyclic antidepressant OR SSRI OR selective serotonin reuptake inhibitor").

Citations were reviewed with an exclusive focus on mature neural tissues because nonneural, immature neural tissues and malignancy-related cells lines have been demonstrated to behave differently with regard to the processes studied here. The sole exception occurred in disease-specific animal models, where stem cells in mature brain were also considered. We considered studies of any methodology but included only models relevant in PD (including PD-specific models and results involving cells or biological processes specifically relevant to PD). Thus, cell culture conditions not typical of PD (e.g., hyperosmotic stress, oxygen deprivation, potassium deprivation, etc.) were also excluded.

We focused on the intracellular processes of interest as specified in the search terms and did not consider studies of other mechanisms unless those studies also considered the targeted processes. For example, intracellular calcium influx and other disease mechanisms were not examined unless they also involved the drugs and processes of interest. Deoxyribonucleic acid (DNA) fragmentation and condensation were required to ascertain apoptosis, and other indices (apoptotic mediator concentration, cell viability) were considered insufficient.

In contrast, in disease-specific animal models, outcomes consistent with putative neuroprotection were considered even if the study did not specifically address the intracellular

targets required for cell and tissue studies, provided that the outcomes were relevant to PD-specific clinical outcomes. We considered studies in rotenone, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), lipopolysaccharide (LPS), and other rodent PD models, a transgenic mouse model relevant to tauopathic parkinsonism (FTDP-17, or frontotemporal dementia with parkinsonism related to tau mutations on chromosome 17), and an amyotrophic lateral sclerosis (ALS) mouse model that examined alpha-synuclein (αSyn).

2.3. Neuroprotective Clinical Trials Search. Clinical studies potentially relevant to determining disease-modifying neuroprotection of drugs in PD, especially those employing neurodegenerative laboratory measures, representing first-line psychotropics were identified through a literature search and bibliographic extension across the literature (PubMed search terms: (neuroprotection OR neuroprotective OR disease modifying OR disease modifying OR disease modification OR progression OR disease progression OR biomarker OR alpha-synuclein OR cerebrospinal fluid OR imaging OR magnetic resonance imaging OR single photon emission computed tomography OR positron emission tomography) AND Parkinson's disease). These terms were joined by the operator "AND" to the drug search terms specified in the section "Posttranscriptional Neurodegenerative Mechanisms Search."

3. Results and Discussion

Chronic psychotropic treatment had some noteworthy effects on the mRNA transcription of PD risk-related genes. For the sake of brevity, gene mRNA expression findings mentioned below generally do not include negative chronic (i.e., at least 3 weeks) treatment studies unless the negative finding is specifically pertinent to the nigrostriatal tract.

Several genes are highly associated with risk ($P < 0.000001$), mentioned here in order of strongest to weakest association with PD risk. It is important to keep in mind that the rank ordering of associated genes can change over time as more data are reported. MAPT (this gene's official designation) is located at q21.1 on chromosome 17 (17q21.1) and is the gene for microtubule-associated protein tau. It has the strongest association with PD risk of all genes. Increased promoter region function, especially with the H1 haplotype, is associated with late-onset PD. Tau and αSyn proteins interact to mutually promote their synthesis and aggregation (see Lithium and Valproate sections below). GBA encodes for acid beta-glucosidase (1q21), mutations of which are linked to PD through an obscure mechanism. MCCC1 (3q27) is the gene for methylcrotonoyl-coenzyme A carboxylase 1 alpha. This protein is involved in nucleotide binding, catalytic activity, ATP binding, biotin binding, and ligase activity and is found in Golgi apparatus and the mitochondrial matrix and inner membrane. Deficiency impairs leucine degradation and produces an organic acidemia with neurological features. CCDC62/HIP1R (12q24.31/12q24) involves two different genes. Coiled-coil domain containing 62 (CCDC62) is involved with estrogen receptor activation, cyclin D1 expression, and cell growth in prostate cancer, and antibodies to this protein develop in various malignancies. This suggests that CCDC62 may play a role in augmenting cellular viability, but its true role in PD awaits discovery. Huntingtin-interacting protein 1-related (HIP1R) is involved in actin binding and receptor-mediated endocytosis. Loss of function is associated with impaired presynaptic function and plasticity, leading to neuronal dysfunction. It appears to protect against polyglutamine toxicity in the transgenic *C. elegans* Huntington model.

Genes less strongly associated with PD risk include BDNF (11p13), the translation of which produces brain-derived neurotrophic factor. BDNF is critical to the survival of striatal neurons. A rare functional G196A (Val66Met) BDNF variant is associated with greater PD severity, earlier PD onset, and cognitive impairment. DRD3 (3q13.3) is the gene for the D3 dopamine receptor. Reduced lymphocyte DRD3 mRNA and the DRD3 2 allele are associated with PD. GSTM1 (1p13.3) encodes glutathione S-transferase mu 1 and is involved in detoxifying electrophilic compounds. The GSTM1 null genotype is linked to PD in the contexts of CYP2D6 poor metabolizer status and solvent exposure. PARK2 (parkin, 6q25.2-q27) mutations are classically associated with sporadic PD and with recessive, early-onset, slowly progressive, Lewy body-negative parkinsonism. Parkin is an E3 ubiquitin ligase enzyme of the ubiquitin-proteasome system, key to disposing of obsolete and toxic proteins. Additionally, parkin confers resistance to oxidative mitochondrial damage and to various apoptogenic stimuli. MAOB (Xp11.23) translation produces monoamine oxidase B. The MAOB G genotype is variably associated with reduced PD risk in Caucasian but not Asian men. CALB1 (8q21.3-q22.1) is the gene for the 28 kilo-Dalton calbindin 1. The CALB1 SNP rs1805874 is linked to PD risk through an unclear mechanism. LRP8 (1p34) is the gene for low-density lipoprotein receptor-related protein 8, associated with the apolipoprotein E receptor. LRP8 knockout increases tau phosphorylation in mice suggesting a relation to MAPT (see above). DRD2 (11q23) encodes the D2 dopamine receptor. Knockout in mice produces parkinsonism, and the TaqIa polymorphism, especially the A1A1 genotype, and 15-allele polymorphism are associated with PD motor fluctuation risk. DRD2-deficient mice manifest akinesia and bradykinesia resembling PD. PARK5 (UCHL1, 4p14) mutations are classically associated with PD onset in the 6th decade. UCHL1 is involved in maintaining ubiquitin monomers for proper functioning of the ubiquitin-proteasome system and has the weakest association with PD risk of the genes considered here. Figures 1 and 2 show the relationship of these genes to the pathobiological processes involved in PD.

For each drug, available findings for gene expression, replicated posttranslational findings (largely cell culture), and animal models are presented. The gene expression effects of psychotropics are considered for PD risk without regard to particular mutations, variants, and genotypes, which are beyond the scope of this paper. It is possible that reduced risk may also translate to slower PD progression, although correlates of risk and disease progression often differ. Replicated findings mostly involved cell culture, with the

majority replicated *across* models (almost half of these *independently* replicated), and nearly half replicated *within* the same model (only valproate induction of αSyn was *independently* replicated). Independent replication within and without models was only evident for lithium and valproate, constituting the two most robustly replicated preclinical findings. Findings from animal models are then detailed. Most PD animal model studies of psychotropics have shown neuroprotective results, including pramipexole, lithium, valproate, lamotrigine, and dextromethorphan, in contrast to desipramine and fluoxetine, which actually shortened mouse survival.

Finally, following the presentation of transcriptomics, cell culture, and animal model findings, clinical trials of drugs constituting first-line psychotropics in human patients with PD are discussed.

3.1. Pramipexole. In the rotenone mouse model of PD, this dopamine D2/D3 receptor agonist decreased αSyn, neuronal death, and motor deficits [10]. In the MPTP rat model of PD, pramipexole inhibited reactive oxygen species (ROS) generation [11]. In the LPS rat model of PD, pramipexole preserved dopamine neurons and reduced ubiquitin upregulation and amphetamine-induced ipsiversive turning, but did not affect the inflammatory response [12]. In a 6-hydroxydopamine rat model of PD, pramipexole increased cell proliferation and survival, neural differentiation, neurogenesis, and epidermal growth factor mRNA in the subventricular zone and increased motor activity [13]. This drug has also increased both BDNF and glial-derived neurotrophic factor (GDNF) in mesencephalic and nigral astrocytic cell culture [14]. Each of these actions is consistent with a reduced risk of PD progression.

3.2. Ropinirole. Although this D2/D3 agonist has been demonstrated to be antiapoptotic in neuroblastoma cell lines, evidence in mature neural tissues was not evident. This drug, however, has been associated with increases in both BDNF and GDNF in rat mesencephalic cell and nigral astrocytic cultures, but not in striatal or cortical astrocytic culture [14]. In a study of mouse astrocytes taken from whole brain, ropinirole increased GDNF but not BDNF [15]. Ropinirole's neurotrophic effect on cultured mesencephalic dopamine neurons was inhibited by the D3 antagonist nafadotride [14]. These findings suggest neurorestorative effects of this drug.

3.3. Antipsychotics. Although it would be ideal to have studies conducted in blood and brain of patients with PD, no such studies have been reported, and the best data that can be obtained for the transcriptional effects of psychotropics has been determined in patients with psychiatric disorders. Chronic antipsychotic treatment downregulated LRP8 and UCHL1 (PARK 5) expression in schizophrenia [16, 17]. Antipsychotic administration downregulated ApoER2 (LRP8) mRNA in peripheral lymphocytes after 6 months of treatment compared to pretreatment baseline in drug-naive patients with schizophrenia [16]. In postmortem prefrontal cortex, chronic treatment was associated with downregulated UCHL1 mRNA relative to matched healthy controls and drug-naïve patients [17]. Since reductions in LRP8 and UCHL1 function are linked to PD, the effects of antipsychotics in these studies would be expected to increase PD risk and, possibly, PD progression (see Figure 2 for LRP8 and PARK5 relation to PD pathobiology).

3.4. Neuroleptics. Neuroleptic inhibition of mitochondrial respiratory Complex I in frontal cortex has been replicated [18, 19], suggesting an increased risk of PD progression and, perhaps, an increased risk of developing the disease.

3.5. Chlorpromazine. Six-month treatment with chlorpromazine upregulated prefrontal and temporal cortical DRD2 mRNA expression in primates [20], an effect that might reduce PD risk and progression.

3.6. Haloperidol. Haloperidol treatment is associated with DRD3, striatal PARK2 (parkin), and striatal DRD2 upregulation and nonstriatal BDNF downregulation. Four weeks of haloperidol induced striatal Park2 [21] and whole brain Drd3 [22, 23] expression in rats, suggesting parkin upregulation specific to the nigrostriatal system. In rat pituitary, 21 days of haloperidol upregulated D2 mRNA expression [24]. Although early striatal studies were negative in rodents [25–27], subsequent studies found upregulated striatal D2 mRNA expression changes after chronic haloperidol treatment [23, 28–32]. Four-week administration upregulated striatal and prefrontal cortical Drd2 expression in rats [22, 32]. In primates, 6-month treatment with haloperidol also upregulated prefrontal and temporal cortical D2 mRNA expression [20]. In contrast, haloperidol downregulated hippocampal and cortical Bdnf expression in rats [33–35], although one hippocampal study showed no change [36].

The replicated mitochondrial effects of haloperidol include Complex I inhibition in frontal cortex [18, 19], Complex II inhibition [37], and apoptosis-inducing factor (AIF) translocation [38].

In sum, while upregulation of striatal PARK2, DRD3, and DRD2 might reduce PD risk, BDNF downregulation, complex I and II inhibition, and AIF translocation would be expected to increase PD risk and could potentially predominate, increasing risk and perhaps progression (Figures 1 and 2). Of course, clinical exacerbation of parkinsonian neurological features effectively contraindicates the use of clinical doses of haloperidol in PD.

3.7. Loxapine. Loxapine administered for 32 days upregulated whole brain D3 [22, 23] and D2 [22, 32] mRNA in rats, thus suggesting an association of loxapine with PD risk reduction.

3.8. Molindone. Six-month treatment with molindone upregulated prefrontal and temporal cortical D2 mRNA expression in primates [20], a finding that is consistent with a potentially reduced PD risk.

3.9. Pimozide. Pimozide upregulated whole brain D3 mRNA in rats after 32 days [22] and upregulated prefrontal and temporal cortical D2 mRNA expression in primates after 6 months [20], suggesting a lowering of PD risk.

3.10. Risperidone. Risperidone [39, 40] treatment for 4 weeks in rats upregulated frontal cortical Maob expression while 6-month treatment upregulated prefrontal and temporal cortical D2 mRNA expression in primates [20]. The D2 result is consistent with a potentially reduced risk for PD. In contrast, risperidone inhibition of frontal cortical Complex I has been replicated, suggesting an increased risk of PD progression [18].

3.11. Olanzapine. Olanzapine upregulated hippocampal and cortical Bdnf [34], frontal cortical Gstm1 [9] and Maob [40], and ventral tegmental Drd2 [41] expression in rats, collectively indicative of reduced PD risk (Figures 1 and 2). Similarly, 6-month treatment with olanzapine upregulated prefrontal and temporal cortical D2 mRNA expression in primates, but in contrast to other drugs, olanzapine did not affect striatal DRD2 expression [20]. These findings nevertheless suggest a lower risk of PD, especially the tegmental finding.

3.12. Quetiapine. The rat literature reveals upregulated prefrontal cortical Bdnf mRNA with quetiapine [42], potentially consistent with reduced PD risk.

3.13. Clozapine. Although rat Bdnf studies reveal both upregulation [34] and downregulation [35] in the hippocampus and cortex with clozapine (10 mg/kg for 28 days) [34, 35], Drd3 expression was upregulated in whole brain after 32 days of treatment [22]. Six-month treatment upregulated prefrontal and temporal cortical D2 mRNA expression in primates, but in contrast to the other drugs, clozapine did not affect striatal DRD2 expression [20]. Nevertheless, clozapine inhibition of frontal cortical Complex I [18] and increase in Complex IV [19] have been replicated, likely indicating an increased risk of PD progression in light of reduced Complex I in PD (Figure 1). Therefore, it is unclear whether clozapine is associated with a reduced or increased risk of PD.

3.14. Aripiprazole. In the ventral tegmental area, aripiprazole increased D2 mRNA expression after 12 weeks of treatment [41], suggesting a reduced risk for PD.

3.15. Lithium. Lithium downregulated BDNF mRNA (while increasing BDNF itself) [43] and did not affect ventral tegmental D2 [44] mRNA expression in rats, suggesting neutral risk for PD. In contrast, replicated findings were confined to decreases in fibrillar tau in transgenic FTDP-17 models [45, 46] and cytochrome c release [47, 48], each associated with the likelihood of a neuroprotective reduced PD progression (Figure 1). In animal models, although in the G93A superoxide dismutase 1 mutant transgenic mouse model of ALS, lithium has been found to decrease both αSyn and ubiquitin aggregation [49]. Although in several different tauopathic FTDP-17 mouse models, lithium decreased tau phosphorylation at a variety of epitopes including Tau1 [45], Ser202 [50], AT8 [46], and PHF1 [46, 50] and decreased tau fibrillization [46] and fibrillar [45] and filamentous [45] tau aggregation. Human FTDP-17 has been particularly associated with Ser202 [51] and AT8 [52] phosphorylation. These models are not only relevant to FTDP-17, but potentially also to PD because tau and αSyn interact to mutually promote their production and aggregation, as explained below (see also Figure 2). Finally, lithium prevented nigrostriatal dopamine neuronal loss in MPTP mice [53]. Each of these findings is consistent with a reduced risk of progression in PD.

Effects on other proteins, such as Aβ and tau, are potentially important to the pathobiology of PD. A referenced discussion is beyond the scope of this paper; however, we have detailed the interactions of these proteins with αSyn elsewhere [4]. Briefly, Aβ and tau each facilitate αSyn aggregation in PD (Figure 2). αSyn also facilitates tau aggregation, and αSyn and tau each independently initiate amyloid formation, further facilitating αSyn aggregation. Furthermore, the enzyme glycogen synthase kinase 3 (GSK-3) promotes αSyn expression, Aβ production, tau phosphorylation, and apoptosis. GSK-3 alleles are associated with PD risk, and GSK-3 inhibitors including lithium and valproate may reduce αSyn. Moreover, αSyn upregulates GSK-3, suggesting that αSyn and GSK-3 mutually upregulate each other, and αSyn can indirectly upregulate Aβ and tau production and aggregation through this mechanism. Still further, each of these proteins (αSyn, Aβ, and tau) can interact at various levels in the pathological chain of events, leading to apoptotic pathway activation, neuronal death, and neuroinflammation. αSyn, Aβ, and tau each inhibit the proteasome, impair mitochondrial function, produce free radicals, and promote apoptosis. Thus, effects on tau and even Aβ can modulate PD pathobiology. In this regard, GSK-3 inhibitors, including lithium and valproate, can have potent effects on αSyn and, potentially, on PD pathobiology (Figure 2).

3.16. Carbamazepine. Carbamazepine upregulated BDNF mRNA expression in rat frontal cortex [54], suggesting a potentially neuroprotective reduced risk of PD.

3.17. Valproate. Replicated findings include increased αSyn [55–57] in several models including cell cultures exposed to 6-hydroxydopamine and glutamate [55, 56] and in the rotenone rat [57]. Valproate has inhibited apoptosis in glutamate [55] and rotenone [57] models. Valproate antiapoptotically decreased monoubiquitylated αSyn [56, 57] and its nuclear translocation [56, 57] and inhibited free radical damage [58]. In the rotenone rat model of PD, valproate increased αSyn, decreased its apoptotic monoubiquitylation and nuclear translocation in both the substantia nigra and striatum, and prevented nigral apoptosis and nigrostriatal neuronal loss, as well as preventing the death and parkinsonian features observed in rotenone rats not treated with valproate [57]. In addition, valproate both protected and increased dopaminergic concentrations in rat mesencephalic mixed neuronal-glial cell cultures after exposures to either LPS or MPTP [59]. Furthermore, valproate increased BDNF and GDNF transcription in astrocytic cell cultures [59, 60]. These actions are consistent with neuroprotection, neuroregeneration, and a reduced likelihood of PD progression (Figures 1 and 2).

It is noteworthy that, like lithium, valproate too is a GSK-3 inhibitor. It can therefore potentially produce potent therapeutic effects on PD pathobiology through attenuation of αSyn, Aβ, and tau proteins, as detailed in the section on Lithium (see also Figure 2). Moreover, valproate is also a histone H3 deacetylase inhibitor (H3 HDACI), and this action has been correlated with neuroprotective increases in αSyn levels [61], possibly upregulating the expression of other risk-attenuating genes while interfering with the repression of risk-associated genes [57]. (Although the role of αSyn in neurodegeneration has been extensively debated and excessive αSyn would seem to predispose to the formation of Lewy bodies that are associated with PD, recent evidence suggests a neuroprotective function of the protein and that it is the depletion of αSyn concentrations and conversion to a monoubiquitylated species traveling to the nucleus that instead promotes αSyn fibrillization and neurodegeneration [57]). Additionally, H3 HDACIs including valproate and dextromethorphan (see Dextromethorphan section) are protective in MPTP and LPS models and appear to protect dopamine neurons by upregulating astrocytic GDNF and BDNF. H3 HDACIs further induce microglial apoptosis (thereby reducing microglial neuroinflammation) and attenuate LPS-induced dopaminergic neurotoxicity [62], again like dextromethorphan. Sirtuins are members of the histone deacetylase family, and inhibition of sirtuin 2 protects cells in PD models [63]. Nuclear αSyn has been shown to inhibit histone acetylation, leading to cellular demise [64], while HDACIs mediate the opposite action. Valproate's GSK-3 and H3 HDACI properties may factor into a neuroprotective effect in PD in a significant way (Figures 1 and 2).

3.18. Lamotrigine. This anticonvulsant has been confirmed to reduce striatal lesions by almost 50% in the MPTP rat model of PD, with an additional 14% reduction when coadministered with CoQ10 [65], consistent with a neuroprotective action and reduced risk of PD progression.

3.19. Antidepressants. Findings replicated across antidepressants include neuroprotective decreases in inflammatory cytokine expression, including IL-1β, IL-6, and TNF-α [66, 67]; however these same drugs (desipramine and fluoxetine) also have reduced survival in MPTP mice [68]. An overall neuroprotective profile for a number of antidepressants suggests that reduced survival may be unique to the MPTP model and that the antidepressants hold the potential to reduce PD progression.

3.20. Amitriptyline. Amitriptyline treatment for at least 21 days in rats upregulated nucleus accumbens shell D3 and striatal D2 mRNA expression [69], consistent with reduced PD risk.

3.21. Imipramine. In rats treated for at least 21 days, imipramine upregulated hippocampal Bdnf [70, 71], nucleus accumbens Drd3 [69], and striatal Drd2 [69] expression, indicative of reduced risk for PD (Figure 1).

3.22. Desipramine. Desipramine given for 21 days upregulated Bdnf in rat hippocampus [43, 72–74] and frontal cortex [74] but, in two studies, downregulated hippocampal mRNA [75] and had no effect on cortex [43, 75]. Treatment for at least 21 days upregulated nucleus accumbens shell D3 and striatal D2 mRNA expression [69]. These findings suggest reduced PD risk with desipramine. Further, decreased neuronal apoptosis in the context of desipramine treatment has been replicated [76, 77], suggesting a neuroprotective diminished risk of PD progression. On the other hand, desipramine treatment in a MPTP mouse model resulted in diminished animal survival [68], perhaps unique to this particular model.

3.23. Nortriptyline. The replication of the finding that this tricyclic antidepressant decreased neuronal apoptosis [76, 78] indicates a neuroprotective potential to reduce PD progression.

3.24. Fluoxetine. Fluoxetine administered for 21 days upregulated Gba, Ccdc62, Hip1R, Bndf, and Uchl1 and downregulated Mapt, Mccc1, Gstm1, and Calb1 expression in rat frontal cortex [8]. In other rat studies of this antidepressant, this same treatment course upregulated Bndf mRNA in frontal cortex and hippocampus [74, 79] (although without effect in one hippocampal study [75]) and in ventral tegmental area and nucleus accumbens shell but not in substantia nigra or striatum [79]. Fluoxetine treatment for at least 21 days upregulated nucleus accumbens shell Drd3 but not striatal Drd2 expression in rats [69]. Overall, the findings suggest a reduced risk of PD (Mapt, Gba, Ccdc62, Hip1R, Bdnf, Drd3, Uchl1) that likely predominates over risk-enhancing effects (Mccc1, Gstm1, Calb1) (Figures 1 and 2), although not specific to the nigrostriatum.

In the MPTP model of PD, however, fluoxetine actually reduced mouse survival [68]. Whether this is unique to this model or will generalize across PD models remains to be determined.

3.25. Sertraline. In rats treated for 21 days, sertraline upregulated BDNF mRNA expression [72], consistent with a reduction in PD risk.

3.26. Paroxetine. Paroxetine administered for 21 days upregulated Bdnf expression [80], consistent with a lower risk for PD.

3.27. Escitalopram. In patients with depression, escitalopram treatment for 12 weeks increased leukocyte BDNF mRNA expression, correlating with serum BDNF level [81] and suggestive of reduced risk for PD.

3.28. Venlafaxine. Venlafaxine upregulated Bdnf expression in rats treated for 21 days [71], suggesting a lowering of risk for PD.

3.29. Duloxetine. In rats treated for 21 days, duloxetine upregulated BDNF mRNA [82, 83], suggestive of a lower risk for developing PD.

3.30. Bupropion. Chronic bupropion downregulated hippocampal expression of Bdnf [75], consistent with an increase in PD risk.

3.31. Diazepam. Decreased cytochrome c release after treatment with diazepam in neurons exposed to t-butyl-hydroxyperoxide [84] has been replicated across models and suggests a dose-dependent neuroprotective reduced risk of PD progression. However, higher doses have promoted apoptosis in other models (see [3] tables published online on journal website).

3.32. Dextromethorphan-Quinidine Combination. Replicated findings in both MPTP and neuroinflammatory LPS models of PD for dextromethorphan include decreased midbrain dopaminergic neuron degeneration in rat mesencephalic cell culture [85, 86] and protection of dopamine concentration, dopamine neurons, and locomotor activity in mice [87].

In MPTP mice, dextromethorphan protected dopamine neurons [87, 88], dopamine concentrations [87], and locomotor activity [87] and reduced glutamatergic excitotoxicity on dopamine neurons [89]. A previous study had not demonstrated protection of dopamine concentrations in this model [89]. Dextromethorphan also protected dopamine concentrations in mice treated with both MPTP and diethyldithiocarbamate [89]. In the methamphetamine mouse model of PD, dextromethorphan protected dopamine neurons and prevented microglial activation [90]. Finally, in the mouse neuroinflammatory LPS model of PD, dextromethorphan protected dopamine neurons, dopamine concentrations, and locomotor activity [87].

Similarly, replicated findings for the dextromethorphan metabolite 3-hydroxymorphinan (3-OHM) include decreased dopamine neurotoxicity in rat mesencephalic cell culture [87, 91] and protection of dopamine neurons, dopamine concentrations, and locomotor activity [87] in MPTP and LPS mouse models. 3-OHM was even more potently protective than dextromethorphan in both models, an effect that was mediated by enhanced astroglial neurotrophic effects and attenuated microglial activation [87].

Dextromethorphan and its 3-OHM metabolite may protect dopaminergic neurons by decreasing neuroinflammation related to microglial activation with its attendant increases in ROS, reactive nitrogen species, and TNF-α, and also by increasing astrocytic neurotrophic support [85–88, 90, 91] (Figure 1). Additionally, dextromethorphan may protect dopaminergic neurons by blocking glutamate excitotoxicity [89] (Figure 2). Furthermore, the 3-hydroxy metabolite has been found to increase histone H3 acetylation (like valproate [55]) and neurotrophins including GDNF and several others (like valproate (see Valproate section) and antidepressants [4]) [87] (Figure 1). GDNF and BDNF have demonstrated neuroprotection of nigrostriatal neurons in several PD models, with GDNF being even more potent than BDNF [4].

Although there were no transcriptomic data available for dextromethorphan/quinidine, it is interesting to consider whether dextromethorphan/quinidine is inadvisable in GSTM1 null genotype patients, since this genotype is associated with PD risk in the context of CYP2D6 poor metabolizer status, and quinidine inhibits CYP2D6. This same concern might also apply to other CYP2D6 inhibitors, including the psychotropics haloperidol, fluoxetine, paroxetine, duloxetine, and bupropion.

3.33. Neuroprotective Clinical Trials. Several studies have attempted to look at markers that can potentially ascertain neuroprotective disease-modifying outcomes. These include clinical trials of ropinirole, pramipexole, and dextromethorphan. Results have been inconclusive to date.

Dopamine agonists constitute first-line neuropsychiatric treatments for apathy and are a mainstay of treatment for PD. Several double-blind parallel group clinical trials have considered course-of-illness slope divergence to ascertain neuroprotective properties in PD. These studies also employed positron emission tomography (PET) and include a 5-year multicenter study of 288 patients with early PD randomized to either ropinirole or L-DOPA [92], the REAL-PET 2-year multicenter trial in 186 patients with PD randomized to ropinirole or L-DOPA [93, 94], a study of 45 patients randomized to ropinirole or L-DOPA [95], and the CALM-PD 2-year multicenter trial in 301 patients with PD randomized to either pramipexole-plus-placebo "L-DOPA" or L-DOPA-plus-placebo "pramipexole" [96]. The ropinirole study involving 288 patients found less dyskinesia with ropinirole but no difference in clinical markers of PD progression [92], and it is not clear that dyskinesia can be considered as a marker of PD pathobiological progression. The ropinirole trial in 45 patients revealed no significant differences between ropinirole and L-DOPA in terms of 18F-dopa uptake deterioration (13% in 28 versus 18% in 9 patients) at 2 years compared to baseline [95]. The CALM-PD study showed less dopaminergic motor complications with pramipexole but greater UPDRS Parkinson scale improvement with L-DOPA or L-DOPA-plus-placebo "pramipexole" [96], yet neuroprotective conclusions are not possible because of uncertain dose equivalence between the two study arms and other limitations. Imaging markers in the REAL-PD investigation revealed slower putamenal (18)F-DOPA (dopaminergic presynaptic terminal marker) signal decline with ropinirole [93, 94] while the CALM-PD study demonstrated reduced β-CIT (dopamine transporter marker) decrement with pramipexole [97]; however alternative pharmacological explanations [98, 99] and other limitations preventing neuroprotective conclusions for the REAL-PET [98, 100] and CALM-PD [99, 101] studies have been detailed.

Dextromethorphan combined with quinidine is a new FDA-approved treatment for pseudobulbar affect. In small clinical trials, dextromethorphan (alone, without quinidine) has improved PD signs in two studies [102, 103] and improved dyskinesia and off time in two others [104, 105], although PD signs did not improve in another study employing a lower dose [106]. None of these studies were designed to assess neuroprotection.

Hence, currently, there is no conclusive clinical evidence of disease-modifying neuroprotection for psychotropics although the clinical trial literature in PD is miniscule.

Table 1: Preclinical effects of psychotropics on PD pathobiology.

	Gene	Protein	Psome	Cmplx	Mt	ROS	Apop	Inflam	Trophins	Animal
Pramipexole		+ αSyn				+			+	+
Ropinirole									+	
Antipsychotics	−									
Neuroleptics	+			−						
Chlorpromazine	+									
Haloperidol	+			−	−					
Loxapine	+									
Molindone	+									
Pimozide	+									
Risperidone	+			−						
Olanzapine	+									
Quetiapine	+									
Clozapine	+			−						
Aripiprazole	+									
Lithium	0	+tau, αSyn								+
Carbamazepine	+									
Valproate		+αSyn				+	+		+	+
Lamotrigine										+
Antidepressants	+									−
Amitriptyline	+									
Imipramine	+									
Desipramine	+						+			−
Nortriptyline							+			
Fluoxetine	+									−
Sertraline	+									
Paroxetine	+									
Escitalopram	+								+	
Venlafaxine	+									
Duloxetine	+									
Bupropion	−									
Diazepam							+			
Dextromethorphan						+			+	+

The effect of psychotropics on PD pathobiology is indicated by a "+" indicating actions consistent with reducing PD risks of onset (gene transcription effects) or progression (other actions). "−" represents actions that are consistent with enhancing risks of onset or progression. "0" indicates neutral risk: *Psome:* proteasome; *Cmplx:* mitochondrial respiratory chain complexes; *Mt:* mitochondrion, *ROS:* reactive oxygen species, *Apop:* apoptosis, *Inflam:* inflammation.

4. Conclusion

Preclinical findings for the specific drugs are summarized in Table 1. Transcriptional effects are subject to the caveats described below. MAPT, GBA, BDNF, and DRD2 genes have the clearest relations to PD risk based on knockout models, null alleles, mutation severity correlations, and haplotype analysis. MAPT, GBA, MCCC1, CCDC62, and HIP1R are most strongly linked to PD in risk association studies. These data indicate that downregulation of MAPT and upregulation of GBA, CCDC62, HIP1R, and perhaps BDNF and DRD2 may reduce PD risk, reflected in Table 1, whereas the effects of transcription regulation of the other genes on PD risk are more tentative. Other preclinical finding caveats are detailed below.

The findings above provide an index of the neuroprotective potential of psychotropics in PD. Fluoxetine had salutary transcriptional effects on 7 of the 10 risk genes studied although its effect on posttranscriptional events is wanting, and it shortened mouse survival in an MPTP model. Drugs with multiple actions that may confer disease-modifying neuroprotection include dextromethorphan, valproate, lithium, and pramipexole. These drugs have neuroprotective effects on αSyn, except that the HDACI dextromethorphan lacked direct data for this protein, and lithium had neuroprotective effects on both αSyn and tau

protein. One potential therapeutic strategy that might be tested in animal models and humans is the combination of valproate with dextromethorphan in attempting to therapeutically modulate H3 HDAC, GSK-3, αSyn, ROS, apoptosis, and trophic factors. Desipramine (transcriptional and antiapoptotic properties) and escitalopram (transcriptional and trophic attributes) might also be worth considering.

In general, most drugs other than bupropion and lithium had beneficial transcriptional effects. This benefit would not necessarily extend to patients with certain gene variants or mutations, where these transcription effects might actually increase PD risk. Most antipsychotics inhibited Complex I, which is already robustly inhibited in PD. Only pramipexole, valproate, and dextromethorphan demonstrated replicated attenuation of ROS while only valproate, desipramine, and nortriptyline showed consistent replicated antiapoptotic activity, although desipramine curiously shortened survival in the MPTP mouse. Whether this result will be obtained in other PD models remains to be elucidated. Pramipexole, valproate, and dextromethorphan have shown replicated protective effects in LPS inflammatory models, although anti-inflammatory mechanisms await replication while a neurotrophic mechanism has been documented [59]. Pramipexole, ropinirole, and valproate have demonstrated replicated increases in both BDNF and GDNF whereas escitalopram increases BDNF and dextromethorphan increases GDNF.

Enthusiasm for applying the transcriptional results must be tempered by limitations including variable PD-risk associations of these genes in different populations, changing gene definitions and gene risk rankings over time, variable effects depending on treatment durations, brain region, and stage of illness, multiple transcriptional effects of drugs with sometimes contradictory risk effects (e.g., fluoxetine), rodent-human translational issues, an incomplete understanding of gene roles in PD pathogenesis, and the uncertainty of how much of the variance in clinical neuroprotection might be accounted for by transcriptional effects. The effects of psychotropics on the expression of these genes should now be studied using RT-PCR, particularly in the substantia nigra and striatum.

There are several caveats in interpreting how well the replicated findings can generalize to and predict clinical translation. These include limitations inherent to a literature review, reporting biases, uneven and unsystematic drug investigation across the various actions of interest, varying predictive validities of PD animal models, and varying drug effects that can depend on dose, treatment duration, apoptogen, neurotoxin, additional disease-modifying mechanisms of action, and stage of illness. A given psychotropic can possess plural neuroprotective and prodegenerative effects and can act simultaneously as both friend and foe, depending on the relative weights of these effects. Additionally, increases in αSyn alone can be either neuroprotective or prodegenerative, depending upon context. An increase in αSyn can lead to proteasomal inhibition, apoptosis, and inclusion formations including Lewy bodies, pathological tau, and Aβ, and yet a rise in αSyn can also effect a neuroprotective response. It appears that monoubiquitylation of αSyn with subsequent translocation to the nucleus may engender apoptosis, in contrast to an otherwise neuroprotective rise in non-monoubiquitylated αSyn [57]. In this regard, evidence that valproate decreased αSyn monoubiquitylation and nuclear translocation in both the substantia nigra and striatum of the rotenone rat is tantalizing [57].

At present, no disease-modifying neuroprotective agents have been conclusively demonstrated to be effective in human clinical trials. These studies have relied on a difference in slope deterioration between treatments to measure progression, rather than the use of neuroprotective paradigms. Clinical trials employing delayed-start or randomized-withdrawal designs [107] are needed to resolve the neuroprotective disease-modifying efficacy of ropinirole, pramipexole, and dextromethorphan in PD. These randomized designs assess disease-modifying effects by comparing two active treatment arms to each other, with the comparator arm receiving placebo for a protracted period followed by active treatment initiation after a delayed period (delayed start), or a switch from active treatment to placebo in the comparator arm substantially before the continued treatment arm is completed (randomized withdrawal). In this way, differences in outcome as a function of differing treatment durations can be assessed. Similarly, studies should be undertaken for the other promising psychotropics that exhibit salutary effects in animal models and have replicated *in vitro* findings. It will be interesting to learn the results of neuroprotective trials for these commonly used treatments in patients with PD.

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Research Article

Neurocognitive Correlates of Apathy and Anxiety in Parkinson's Disease

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Parkinson's disease (PD) is associated with various nonmotor symptoms including neuropsychiatric and cognitive dysfunction. We examined the relation between apathy, anxiety, side of onset of motor symptoms, and cognition in PD. We hypothesized that PD patients would show different neuropsychiatric and neurocognitive profiles depending on the side of onset. 22 nondemented PD patients (11 right-side onset (RPD) with predominant left-hemisphere pathology, and 11 LPD) and 22 matched healthy controls (NC) were administered rating scales assessing apathy and anxiety, and a series of neuropsychological tests. PD patients showed a higher anxiety level than NC. There was a significant association between apathy, anxiety, and disease duration. In LPD, apathy but not anxiety was associated with performance on nonverbally mediated executive function and visuospatial measures, whereas, in RPD, anxiety but not apathy correlated with performance on verbally mediated tasks. Our findings demonstrated a differential association of apathy and anxiety to cognition in PD.

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the loss of nigrostriatal and mesocortical dopaminergic projections from the brain stem and limbic cortex to the basal ganglia and neocortex. The basal ganglia and related structures are critical structures in parallel frontal subcortical circuits involved in regulation of cognition, emotions, and behavioral activation [1–3]. While primarily characterized as a movement disorder, PD is associated with various nonmotor symptoms [4–6], including cognitive dysfunction [7–10] and neuropsychiatric symptoms, such as apathy [11–17] and anxiety [18–20]. Recent neuroimaging and neuropsychological findings raise the question of the role of apathy and anxiety in PD-related cognitive dysfunction, as these neuropsychiatric conditions reflect dysfunction in brain areas involved in PD.

Typically, early motor signs of PD start on one side of the body, and side of onset remains a significant clinical and neuropathological factor in both clinical management and the study of PD. PD patients with symptoms starting on the right side of the body (RPD) have greater inferred left hemisphere pathology and those with left-side onset (LPD) have greater inferred right hemisphere pathology [21]. The motor symptoms of PD are associated with asymmetrical depletion of dopamine in the substantia nigra of the midbrain across the range of disease severity. These changes in the substantia nigra lead to asymmetrical dysregulation of the striatum, which may in turn lead to further asymmetrical dysfunction of neural circuits including the basal ganglia and cortical projection areas (reviewed in [8]). This neuropathological asymmetry remains evident even with PD progression [22], and initial motor asymmetry predicts a range of motor and neuropsychiatric deficits in PD patients [21, 23]. Specific cognitive problems are also related to side of initial motor onset: LPD versus RPD [8].

Cognitive impairments to a various degree have been documented in many patients with PD. The most common

cognitive domains affected are attention and executive function (planning, problem solving, verbal fluency) and visuospatial function. While language abilities remain generally intact, mild naming deficits may be present in some patients [24]. Previous work demonstrated that the degree of impairment and specificity of cognitive domain affected by the disease is mediated by the side of initial motor onset, which is presumably predetermined by asymmetrical dopamine depletion in PD (reviewed in [8]). Thus, cognitive domains predominantly subserved by the left hemisphere, such as verbally mediated tasks of executive function and verbal memory would be more affected in RPD than LPD, and vice versa. For instance, RPD patients showed poorer verbal memory performance than do those with LPD, who were more impaired on visual memory [7].

Apathy, a reduction in self-initiated cognitive, emotional, and behavioral activity, is a common clinical feature of prefrontal and basal ganglia lesions or dysfunctions [25]. Apathy was documented following direct damage to the prefrontal cortex [26–28]. It is also a common feature of frontostriatal diseases, such as PD [11–14], Huntington's disease [29–31], and HIV [32–37]. Apathy in PD is attributed to nigrostriatal dopaminergic loss in basal ganglia [38] and is considered one of the core features of PD [17], occurring in up to 70% of PD patients [39]. While apathy symptoms may overlap with those of depression, the two conditions have been shown to be reliably differentiated in patient samples [16, 40]. Apathy was related to cognitive dysfunction in PD and other frontostriatal disorders. Specifically, apathy was associated with more severe cognitive dysfunction, specifically executive dysfunction in PD [13, 14, 41]. Studies of HIV have documented associations between the presence of apathy and poor performance on measures of executive function, suggesting that apathy and HIV-related cognitive dysfunction may share common neurophysiological substrates [3, 42]. Apathy is more common in patients with right than left hemisphere damage [14, 43]. Neuroimaging studies showed that apathy was correlated with decreased right temporoparietal perfusion in Alzheimer's patients [44] and with decreased gray matter volume in the right anterior cingulate in older adults [45]. In PD, apathy was correlated with low gray matter density in bilateral inferior frontal and inferior parietal gyrus, right cingulate and right precuneus in one study [46] and with low volume of the right medial temporal lobe in another study [12].

Anxiety is also a very common and yet under studied nonmotor symptom of PD. Prevalence of anxiety disorders in PD varies, with estimates up to 49% [18, 47–49]. Previous studies documented a negative impact of anxiety symptoms on severity of PD [49], subjective motor symptoms [50] and on health-related quality of life in PD [51, 52]. Anxiety also may be associated with depression in PD. Some authors reported overlapping symptoms of depression and anxiety in PD patients [49]. However, dissociation of anxiety and depression in PD was also documented by several studies [53]. Previous studies provide support to the notion that anxiety and depression refer to different neural mechanisms in patients with PD (reviewed in [53]). Earlier studies reported anxiety associated with various cognitive deficits [54–56], though few studies have investigated the effect of anxiety on cognition in PD. One study found that PD patients with symptoms of anxiety demonstrated poorer performance of various measures of executive functioning, attention, processing speed, and episodic memory [57]. These findings remained significant after symptoms of depression were controlled. Ryder and colleagues also reported a negative association between anxiety and cognitive performance in PD [58]. Anxiety is a common feature of left hemisphere involvement [59–61]. Lesion studies showed that individuals with left hemisphere lesions may be particularly at risk of developing anxiety after stroke [62]. Anxiety was also associated with greater left-hemisphere activation in healthy adults [63]. More recently, anxiety was associated with bilateral middle frontal, anterior cingulate, and left parahippocampal/amygdala region in healthy adults [64]. Another study of healthy adults that reported left amygdala volumes significantly predicted anxiety scores and found an overlap between areas associated with both amygdala volume and anxiety scores in the orbitofrontal cortex and the left inferior parietal region [65]. Apathy and anxiety both have a very significant effect on quality of life and substantially increase patient disability [52, 66, 67]. Understanding their effect on cognition, elucidating underlying neural mechanisms and evaluating the implications for management of these neuropsychiatric symptoms PD are urgently needed.

This study aimed to further elucidate the phenomenology of neuropsychiatric symptoms in PD by (1) assessing the effect of neuropsychiatric status on cognitive function, in particular, the relation of apathy, anxiety, and cognition; and (2) relating them to the hemispheric asymmetry of initial presentation (side of onset of motor symptoms). Previous neuroimaging studies demonstrated that different neuropsychiatric conditions are differentially mediated by lateralized brain areas (as outlined above), which led us to expect that the expression of apathy and anxiety in PD would be lateralized as well. We hypothesized that PD patients would show different neuropsychiatric and neurocognitive profiles depending on the side of disease onset, with LPD exhibiting cognitive deficits predominantly in the nonverbal domain, which would be related to apathy, and RPD showing deficits predominantly in verbal domain, which would be related to anxiety. Apathy and anxiety are important determinants of quality of life in PD. Early detection and treatment of both conditions may enhance patients' everyday functioning and thus protect their quality of life.

2. Methods

2.1. Participants. The participants included 22 nondemented individuals with PD and 22 normal control adults (NC), who were matched on sociodemographic variables (see Table 1). All participants scored 28 or higher on the Mini-Mental State Examination [68] and were not demented. Participants with PD were recruited from the Parkinson Clinic of the Department of Neurology, Boston Medical Center, and through local support groups. Healthy age-matched control participants (NC) were recruited for the study from the community.

Table 1: Demographic and clinical variables in PD and NC participants. Means (SD) are reported unless otherwise indicated.

	NC	RPD	LPD
N	22	11	11
Age	61.3 (6.9)	63.2 (6.0)	61.3 (6.2)
Years of Education	16.0 (1.9)	15.5 (2.2)	15.9 (3.0)
M : F	11 : 11	6 : 5	5 : 6
MMSE (total)	29.8 (0.5)	29.1 (0.9)	29.5 (0.8)
BDI-II (total)	4.6 (4.1)*	7.3 (3.5)	7.0 (4.0)
Disease Duration (Years)	n/a	8.4 (3.7)	9.0 (4.0)
Hoehn and Yahr stage^	n/a	2 (2-3)	2 (2-3)
LED	n/a	475.2 (294.4)	497.5 (329.7)

BDI-II: Beck Depression Inventory-II.
* Significantly different from PD groups (Ps < 0.04).
^Median (range).
n/a: not applicable.
LED: levodopa equivalent dosage.

The research was approved by Boston University's Institutional Review Board. Participants were required to be native speakers of English. Exclusion criteria included coexisting cancer, serious cardiac disease, other serious chronic medical illness, prior intracranial surgery, history of traumatic brain injury, psychiatric (not including diagnosis of depression or anxiety) or neurological diagnoses other than PD, history of alcoholism or other drug abuse, history of eye disease or other visual abnormalities, and use of psychoactive medications, except for use of antidepressants and anxiolytics in the PD group, which are commonly prescribed. PD clinical staging was determined by their neurologist based on the widely used index of motor disability, Hoehn and Yahr scale [69]. All PD participants were stages II-III (mild to moderate bilateral). The average duration of disease was 8.7 years (SD = 3.8). PD diagnosis was made by patients' neurologists, using UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria [70]. Side of motor symptom onset was obtained by patient report as well as from the patient's neurologist records. Eleven patients had right body side onset of motor symptoms (RPD: 6 men, 5 women), and 11 had left-side onset (LPD: 5 men, 6 women). RPD and LPD groups did not differ in age, education, mental status, Hoehn and Yahr stage, or disease duration. There were no group differences between male and female PD participants in age, education, mental status, Hoehn and Yahr stage, or disease duration. All PD participants received daily dopamine replacement therapy and/or dopamine receptor agonists. Levodopa equivalent dosages (LED) were calculated based on previous reports with LED: (regular levodopa dose × 1) + (levodopa controlled-release dose × 0.75) + (pramipexole dose × 67.0) + (ropinirole dose × 16.67) + (rotigotine × 16.67) + (pergolide dose and cabergoline dose × 67.0) + (bromocriptine dose × 10) + ([regular levodopa dose + levodopa controlled-release dose × 0.75] × 0.25) if taking tolcapone or entacapone [71]. There were no significant differences in RPD versus LPD patient groups in levodopa dose equivalents and dopamine agonists. None of the PD participants were taking anticholinergic medications, and three were taking some form of sleep medication. PD participants were tested while being administered their antiparkinsonian medications (in their "on state").

2.2. Procedure. Before participating, each individual provided informed consent in accordance with regulations of the Boston University Institutional Review Board. All participants were administered standardized measures of neuropsychiatric functioning, and a series of neuropsychological measures sensitive to PD-associated cognitive impairments. Cognitive tests were chosen to assess a range of cognitive abilities in verbal and nonverbal domains, to specify the role of neuropsychiatric symptoms in cognitive functioning in nondemented individuals with PD. All tests were administered and scored according to standard procedures. Because the PD and NC groups were matched on age, education, and male : female ratio, we compared and reported raw scores for all tests.

2.2.1. Neuropsychiatric Status Assessment. We assessed anxiety and apathy using standardized self-report measures.

Apathy was assessed using the modified 14-item *Apathy Evaluation Scale* (AES) [11, 72]. Items are rated on a 0-to-3 Likert scale. Scores range from 0 to 42, with higher scores indicative of more severe apathy level. Sample items include, "Are you interested in learning new things?" and "Are you indifferent to things?" AES and its modified version were reported to have excellent psychometric properties and have been used in studies of Parkinson's disease [11, 13] and other frontostriatal disorders [3, 36, 73]. Total score was the dependent measure.

The Beck Anxiety Inventory (BAI) [74] is a 21-item self-report instrument that assesses the existence and severity of symptoms of anxiety. There is a four-point scale for each item ranging from 0 to 3. Total score in the range of 0–13 is considered indicative of minimal or no depression, 14–19 is mild, 20–28 is moderate, and 29–63 is severe [75]. The BAI was reported to differentiate well between anxious and nonanxious groups in a variety of clinical settings.

The Beck Depression Inventory, Second Edition (BDI-II) [76], is a 21-item self-report instrument that assesses the existence and severity of symptoms of depression as listed in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) [77]. There is a four-point scale for each item ranging from 0 to 3. Total score in the range of 0–13 is considered indicative of minimal or no depression, 14–19 is mild, 20–28 is moderate, and 29–63 is severe.

2.2.2. Cognitive Functioning Assessment. The neuropsychological series included a number of tests that we expected to be sensitive to frontostriatal and parietal dysfunction (attention, executive function, visuospatial ability) as well as tests that we expected would elicit relatively unimpaired performance in the nondemented PD group (naming abilities and memory). The focus of interest was also on the dissociation between the performance on the verbally and nonverbally

mediated tasks, which would be most relevant for the association between the side of onset and cognitive functioning in nondemented persons with PD.

Verbal Domain

(i) *Controlled Oral Word Association Test* [78]. This is a standardized test of verbal (phonemic) fluency, in which participants were required to generate words beginning with a particular letter (F, A, S). Total number correct within a 60-s time period for each condition was recorded.

(ii) *Digit Span*, Wechsler Memory Scale III [79], is a standardized measure of efficiency of attention (Forward Span) and working memory (Backward Span) in verbal domain [61]. The standard total score was used for the group comparison.

(iii) *Clock Reading Test* [27]. The participants are asked to identify and "read" the time shown on each of the 10 clocks presented on a standard paper. Total number of correct responses and time to completion is recorded.

(iv) *The Boston Naming Test* (BNT) [80] is a test of confrontation naming, in which the participant names 60 black and white line drawings of objects presented one at a time. The total number correct was recorded.

(v) *California Verbal Learning Test-II* (CVLT-II) [81] is a test of list-learning verbal memory. Immediate Recall, Delayed Recall, and number of errors were recorded.

Nonverbal Domain

(i) *Raven's Coloured Progressive Matrices* (RCPM) [82]. This is a standardized measure assessing visuospatial skills and reasoning ability. The task is to choose one of six possible completions of an incomplete pattern matrix. Total score (the number correct out of 36 items) was recorded.

(ii) *The Trail Making Test* (TMT) [83] is a standardized test of psychomotor speed and executive functioning. Trails B subtest is a measure of combined visual search, psychomotor speed, and cognitive flexibility, assessing the ability to shift and maintain the response set, where participants sequentially alternate between alpha-numeric sequences (1-A-2-B, etc.). Time to completion was used for the group comparisons.

(iii) *Spatial Span*, Wechsler Memory Scale III [79], is standardized measure of efficiency of attention and working memory (Backward Span) in nonverbal domain [61]. The standard total score was used for the group comparison.

(iv) *Visual Symbol Search Test* (VS) [84] provides a measure of visual scanning abilities and sustained attention. Participants search and cancel the target symbol in the nonverbal array. Time to completion was used for the group comparison.

(v) *Rey-Osterrieth Complex Figure* Test (ROCF) [85]. In an assessment of visuospatial memory, participants were asked to recall the abstract figure image by redrawing it immediately after copying (incidental) and again after 25 minutes (delayed recall). We employed the 36-point scoring system evaluating the presence and accuracy of the 18 elements of the ROCF, and a total score was recorded.

2.2.3. Statistical Analyses. To analyze differences between PD and NC groups, independent samples t-tests (2-tailed) were used. Pearson correlations were performed to examine associations between apathy and anxiety ratings and neuropsychological performance within the PD and NC groups separately. Multiple regression analyses were performed to examine the relative contribution of neuropsychiatric and disease-related variables to cognitive functioning in PD, using apathy and anxiety total scores and disease duration as predictors, and neuropsychological test scores as criterion variables. Analyses of performance of men and women in both the PD and NC groups revealed no significant differences in neuropsychological profile or mood ratings, and data were accordingly collapsed across gender.

3. Results

This study used a within-subject design, with each participant receiving all assessments. The results are divided into two sections: the first section presents findings regarding the effects of PD on neuropsychiatric status and cognitive function; the second section relates neuropsychiatric status to cognitive performance, and more specifically to the hemispheric asymmetry of initial presentation (side of onset of motor symptoms).

3.1. Effect of PD on Neuropsychiatric Status and Cognitive Function

Apathy. Independent groups t-tests revealed that the PD participants reported significantly more apathy symptoms than the NC group ($F(1, 43) = 0.53$, $P < 0.04$). AES mean total score was 8.4 (SD = 3.9) for PD and 6.3 (SD = 2.9) for NC. We also conducted RPD and LPD subgroup comparisons that revealed significant differences between the two PD subgroups ($F(1, 21) = 0.11$, $P < 0.02$), with RPD mean total AES score = 10.42 (SD = 3.3) and LPD score = 6.9 (SD = 3.8). Apathy ratings (AES total score) significantly correlated with disease duration (years since onset) ($r = 0.57$, $P < 0.016$).

Anxiety. The PD group reported significantly more anxiety symptoms than the NC group ($F(1, 43) = 1.49$, $P < 0.03$). BAI mean total score was 9.3 (SD = 8.1) for PD and 4.9 (SD = 5.2) for NC. There was a significant association between anxiety (BAI total score) and disease duration (years since onset) ($r = 0.58$, $P < 0.015$). PD subgroup comparisons did not

Table 2: Neuropsychological performance; raw score mean values (SD).

	NC	RPD	LPD
Verbal Domain			
FAS total	50.2 (16.3)	45.2 (14.4)	41.5 (7.5)*
Digit span forward total	12.1 (2.2)	10.6 (1.9)	11.2 (1.8)
Digit span backward total	8.8 (2.6)	6.6 (2.8)*	6.8 (1.6)**
Clock reading total	48.5 (18.8)	64.2 (15.3)*	62.5 (24.1)
BNT total correct	56.4 (3.2)	57.3 (3.5)	55.9 (5.1)
CVLT-II immediate recall total	11.4 (2.2)	11.7 (3.5)	11.3 (3.2)
CVLT-II delayed recall total	10.8 (2.8)	11.1 (3.5)	8.9 (3.7)
Nonverbal Domain			
RCPM total	34.1 (2.1)	31.1 (4.3)**	31.8 (3.0)*
TMT B time	66.8 (31.4)	86.8 (40.3)	99.3 (90.9)
Spatial span forward total	8.4 (1.7)	7.5 (1.9)	8.0 (1.1)
Spatial span backward total	7.8 (1.8)	7.2 (1.2)	7.3 (2.2)
VS search time	82.2 (21.7)	130.9 (45.2)**	137.2 (93.7)**
ROCF immediate recall total	17.1 (6.5)	15.6 (7.3)	17.8 (7.0)
ROCF delayed recall total	17.9 (6.1)	15.3 (8.3)	17.0 (7.2)

Significantly different from NC group: $^{*}P < 0.03$, $^{**}P < 0.007$.
FAS: Controlled Oral Word Association Test (F, A, S),
BNT: Boston Naming Test,
CVLT-II: California Verbal Learning Test-II,
RCPM: Ravens Coloured Progressive Matrices,
ROCF: Rey-Osterrieth Complex Figure,
VS: Visual Symbol Search.

show significant difference between RPD and LPD on BAI ($P > 0.46$).

Cognitive Performance. To examine whether the PD group exhibited cognitive deficits compared to the NC group, we conducted independent groups t-tests across neuropsychological assessments. The PD group performed more poorly than the NC group on a number of tests. Significant group differences were observed on verbally and nonverbally mediated measures of executive and visuospatial functioning (see Table 2).

3.2. Relation between Neurocognitive and Neuropsychiatric Status and Side of Onset. Further analyses revealed correlations between neuropsychiatric (AES and BAI) and neuropsychological measures (Table 3). The cognitive differences remained significant when controlling for apathy (all Ps < 0.042) and for anxiety (all Ps < 0.035). As predicted, we observed a different pattern of performance by the two PD subgroups. In LPD, apathy but not anxiety was associated with performance on *non-verbally* mediated executive function and visuospatial measures [TMT B, Spatial Span, and Visual Search], whereas in RPD, anxiety but not apathy significantly correlated with performance on *verbally* mediated tasks [BNT, CVLT, Clock Reading, and FAS] (Table 3).

Table 3: Correlations between RPD and LPD neuropsychological performance and apathy (AES) and anxiety (BAI) ratings.

	Apathy	Anxiety
Verbal domain		
RPD		
FAS total correct	ns	−0.74*
Clock reading total errors	ns	0.84**
Clock reading impulsive errors	ns	0.89**
BNT total correct	ns	−0.84**
CVLT errors (intrusions)	ns	0.89**
Nonverbal domain		
LPD		
TMT B time	0.73*	ns
TMT B errors	0.64*	ns
Spatial span forward total	−0.68*	ns
Spatial span backward total	−0.69*	ns
VS search time	0.65*	ns
VS search errors (omissions)	0.70*	ns

$^{*}P < 0.025$; $^{**}P < 0.005$.
TMT: Trail Making Test,
VS: Visual Symbol Search.

4. Discussion

We examined the effect of PD on neuropsychiatric status and its relation to side of onset of motor symptoms and cognition in nondemented individuals with PD. First, PD patients reported significantly more apathy and anxiety symptoms than the NC group. There were also PD-related changes in multiple cognitive domains. The affected domains included attention, executive function, and visuospatial function, which is reflective of frontostriatal and parietal dysfunction associated

with PD. Second, the extent of apathy and anxiety significantly correlated with performance on neuropsychological measures of attention, executive, and visuospatial function. Third, we observed different neuropsychiatric and neurocognitive profiles depending on the side of disease onset, in support of our hypothesis. Specifically, we had predicted that patients with LPD would exhibit cognitive deficits predominantly in the visuospatial domain, which would be related to apathy. In contrast, RPD would show cognitive deficits in verbal domain, which would be associated with anxiety symptoms.

To our knowledge, this is the first study to demonstrate a differential association of apathy and anxiety to cognitive dysfunction in PD, in relation to the side of onset of motor symptoms.

Apathy and anxiety are common clinical features of PD, and both are important predictors of everyday functioning and quality of life. Previous neuroimaging and neuropsychological studies related these neuropsychiatric conditions to PD-associated dysfunction. However, the role of apathy and anxiety in cognitive dysfunction and their underlying neurophysiological substrates remain a subject of ongoing investigation. Several studies related apathy to cognitive dysfunction in PD and other frontostriatal disorders (reviewed earlier in this paper). While anxiety was also associated with various cognitive deficits [54–56], there have been only a few studies that investigated the effect of anxiety on cognition in PD [58]. We assessed the effect of both apathy and anxiety on cognitive function in PD; in particular, the relation of apathy and anxiety to lateralized cognitive domains (verbal versus visuospatial).

Consistent with previous literature, our PD patients reported significantly more apathy and anxiety symptoms than the NC group, implicating disruption of specific frontostriatal neural pathways. Also, as expected, we observed PD-related changes in multiple cognitive domains in our sample of nondemented patients, including attention, executive function, and visuospatial function. These findings provide additional support to earlier work, which suggested that the higher prevalence of apathy and anxiety in PD, as compared to general population, reflects PD-related dysfunction of frontostriatal systems.

As suggested by previous research (reviewed above), various neuropsychiatric conditions are differentially mediated by lateralized brain areas, which led us to hypothesize that the expression of apathy and anxiety in PD also would be lateralized. Specifically, we expected that PD patients would show different neuropsychiatric and neurocognitive profiles depending on the initial side of motor onset. We predicted that LPD patients would exhibit cognitive deficits predominantly in the visuospatial domain, which would be related to apathy. We also examined the potential mediating influence of anxiety on cognitive performance in PD. Specifically, we expected that RPD patients would show cognitive deficits predominantly in the verbal domain, which would be related to anxiety.

As predicted, we observed different neuropsychiatric and neurocognitive profiles in our PD subgroups. Apathy and anxiety differentially correlated with performance on neuropsychological measures. The lateralized cognitive domain (verbal versus visuospatial) was the mediating factor in this paradigm. The observed dissociation between apathy and anxiety and distinct cognitive domains suggested anatomically and functionally distinct neural substrates. Consistent with our hypotheses, in LPD, apathy but not anxiety was associated with performance on nonverbally mediated executive function and visuospatial tasks. This finding is consistent with earlier reports of apathy being related to right-hemisphere dysfunction [12, 14, 43, 46]. In RPD, by contrast, anxiety but not apathy significantly correlated with performance on verbally mediated tasks. This finding provides additional support to lesion studies and neuroimaging reports relating anxiety to left-hemisphere dysfunction [59–61, 63, 65]. Taken together, our results demonstrated a differential association of apathy and anxiety with cognition in PD.

In this study, we observed no significant differences between the RPD and LPD subgroups in anxiety ratings, and higher levels of apathy in the RPD group as compared to LPD. The lack of group differences in anxiety level and higher rate of apathy in the RPD group may potentially reflect variations in the degree of lateralized pathology within each subgroup in our nondemented PD sample. Future investigations with larger patient samples and a wider range of disease duration and disease characteristics may shed light on changes in the lateralization and expression of neuropsychiatric deficits across time, as PD-associated neuropathological changes may become less lateralized with disease progression. Longitudinal studies are needed to address the effect of the treatment of apathy and anxiety on cognitive function and quality of life in PD.

Although limited by the size of our study sample, our results nevertheless indicate a significant relation between neuropsychiatric status and disease duration in nondemented PD. We found that apathy and anxiety ratings were associated with PD duration. The identification and treatment of these neuropsychiatric conditions in patients with PD is very important, as both apathy and anxiety have significant impact on quality of life and substantially increase patient disability [66, 67]. Apathy and anxiety are treatable conditions, and timely screening and intervention may protect the quality of life and reduce disability in individuals with PD.

In conclusion, this study examined the association between neuropsychiatric symptoms and cognitive function in non-demented individuals with PD. Our findings supported the notion that the higher rate of apathy and anxiety in PD than in the general population may reflect a direct consequence of the damage to the frontostriatal system and its cortical connections, resulting in both neuropsychiatric and neurocognitive deficits. Examination of the relation between apathy and anxiety and distinct cognitive domains suggested anatomically and functionally distinct neural substrates. The observed dissociation between RPD and LPD neuropsychiatric status and cognitive performance also points to distinct underlying neural substrates within corticostriatal-thalamocortical circuits. These results indicate specific relations of apathy and anxiety to cognition in PD. Finally, we found that

apathy and anxiety ratings were associated with disease duration. The results of this study stress the importance of identifying and treating these neuropsychiatric conditions in PD patients.

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Review Article

Frontostriatal Cognitive Staging in Parkinson's Disease

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Cognitive impairment and behavioural disorders are often encountered in subjects with Parkinson's disease (PD). A simple PD-related frontostriatal cognitive dysfunction (PDFCD) staging is proposed. Executive dysfunction and mental fatigue (stage I), depression/anxiety (stage IIa), apathy/pain (stage IIb), and dementia (stage III) reflect a sequential process of dopamine depletion occurring in different regions of the striatum (stages I and II) and the frontal cortex (stage III). In addition to these nonmotor manifestations present in the unmedicated (OFF) state, the PDFCD model also predicts a number of complications related to dopaminergic treatment (ON state), from impulse control disorders (stages I and IIa) to hallucinations (stage IIb) and psychosis (stage III). Although the model admittedly needs further refinements, it provides a framework for hypothesis testing and may help clinicians optimize therapeutic strategies.

1. Introduction

Parkinson's disease (PD) is biochemically characterized by dopamine depletion [1, 2]. Although the loss of dopamine is particularly severe in the putamen, which explains the motor manifestations of the disease, other dopaminergic projections are also affected and contribute to the development of cognitive impairment and neuropsychiatric disorders [3, 4]. Thus, some degree of executive dysfunction is a virtually constant finding in PD, even in the early stages of the disease [5]. Apathy, depression, anxiety, and fatigue are present in one third of patients [6], and pain is also common [7]. Similarly, it has been estimated that approximately one third of PD subjects end up developing dementia [3, 4]. In this review, I will use a simple model to correlate these nonmotor manifestations of the disease with different stages of frontostriatal dysfunction caused by dopamine depletion sequentially occurring in different regions of the striatum and the frontal cortex [8–11].

The PD-related frontostriatal cognitive dysfunction (PDFCD) staging here proposed (Figure 1) assumes that dopamine-dependent frontostriatal functioning follows an inverted U-shaped dose-response curve (Figure 2). The PDFCD model is mostly based on neuroimaging data and clinical observations, and offers stage-specific clinical predictions off and on dopaminergic medication.

2. Dopamine Depletion and Dysfunction of Frontostriatal Loops

PD is characterized by a gradient of dopamine depletion in the striatum, with the putamen being the most affected region, followed by the dorsal caudate, and then the ventral striatum (ventral caudate and nucleus accumbens) [1, 2]. A combination of PD-specific and aging-related dopamine depletion [12, 13] determines the degree of cognitive/behavioural dysfunction.

Three major anatomical and functional frontostriatal loops are proposed to be sequentially affected in PD: first, the motor loop, which connects the supplementary motor area with the putamen; second, the cognitive loop, which connects the dorsolateral prefrontal cortex (DLPFC) with the dorsal caudate nucleus; and third, a "complex" limbic loop, with connections between the orbitofrontal cortex (OFC) and the ventral caudate nucleus, and between the anterior cingulate cortex (ACC) and the nucleus accumbens. These three functional frontostriatal loops have been well characterized both theoretically and experimentally [8–11].

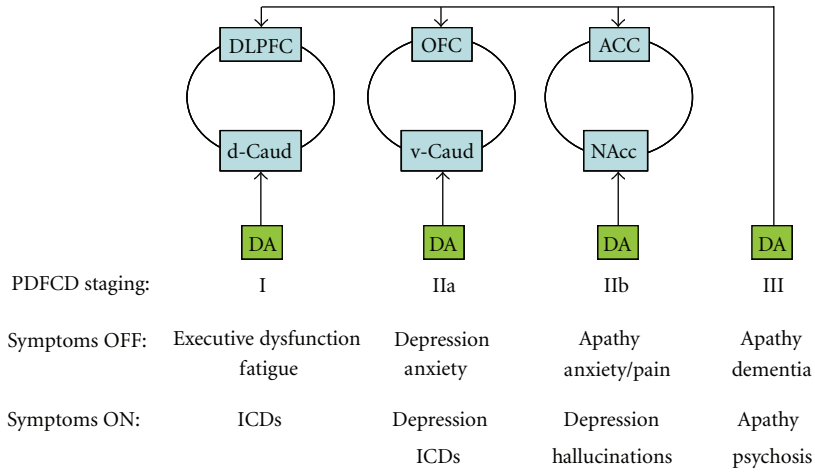

Figure 1: Parkinson's disease-related frontostriatal cognitive dysfunction (PDFCD) staging. Three major frontostriatal loops are shown: (1) the loop connecting the dorsolateral prefrontal cortex (DLPFC) with the dorsal caudate nucleus (d-Caud), (2) the loop connecting the orbitofrontal cortex (OFC) with the ventral caudate nucleus (v-Caud), and (3) the loop connecting the anterior cingulate cortex (ACC) with the nucleus accumbens (NAcc). Dopamine (DA) projections for these loops, as well as the direct dopaminergic projection to the frontal cortex, are schematically shown. Major symptoms, OFF and ON dopaminergic treatment, are detailed. ICDs: impulse control disorders.

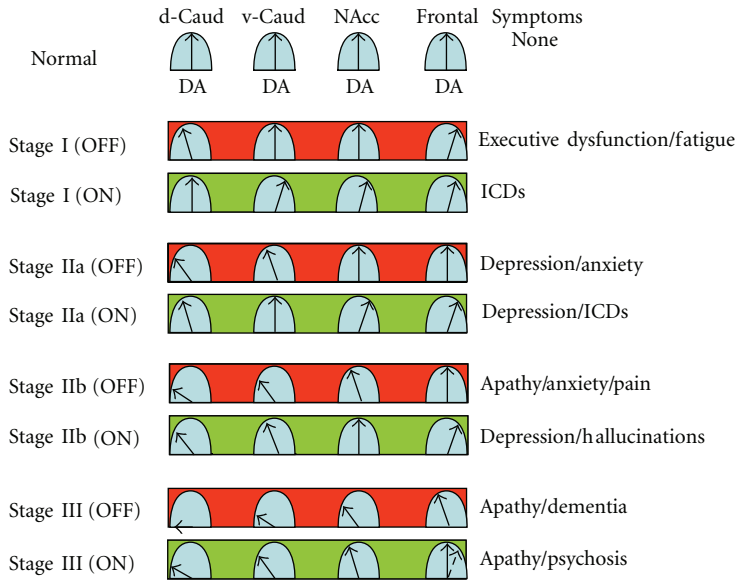

Figure 2: Parkinson's disease related frontostriatal cognitive dysfunction (PDFCD) staging with region-specific dopamine (DA) levels. Dopamine-related frontostriatal functioning is assumed to follow an inverted U-shaped dose-response curve. Predicted stage-specific dopaminergic function, both off and on dopaminergic treatment, is shown for dorsal caudate (d-Caud), ventral caudate (v-Caud), nucleus accumbens (NAcc) and frontal cortex. In the ON state, the inverted U-shaped curves represent DA levels if the patient is on levodopa, and DA tone if the patient is on a dopamine agonist. The direct dopaminergic projection to the frontal cortex seems to be initially upregulated, but with limited capability to increase further the dopaminergic tone in response to dopaminergic treatment (see text for details). ICDs = impulse control disorders.

In more advanced PD, the direct dopaminergic projection to the frontal cortex becomes also affected, leading to cortical dopamine depletion [14, 15]. There is evidence that the release of dopamine, at both the striatal and cortical level, facilitates loop functioning [8–11]. Alterations in the motor loop are crucial because they serve to make the clinical diagnosis, signalling that PD pathology has reached midbrain dopamine cells [16]. However, the PDFCD model only applies to the cognitive/limbic loops and the direct dopaminergic projection to the frontal cortex.

In the early stages of PD, frontal lobe dysfunction is assumed to reflect cortical "deafferentation" in relation

to striatal dopamine depletion. At later stages, cortical dopamine depletion likely contributes to frontal lobe impairment. In keeping with this notion, dementia in PD is related to the loss of dopamine cells in the medial part of the substantia nigra pars compacta [17] and ventral tegmental area [18], regions that originate direct dopaminergic projections to the cortex. Interindividual variability in the time course and degree of dopamine depletion in different striatal and frontal regions may explain the wide range of clinical manifestations encountered in PD. Although the PDFCD model is only based on striatal and frontal dopamine depletion, cortical Lewy body pathology, which typically occurs in advanced PD [16], will eventually contribute to the development of frank dementia [16, 19].

3. PDFCD Stage I: The Frontostriatal Cognitive Loop

3.1. Functional Analysis. The frontostriatal cognitive loop (DLPFC—dorsal caudate nucleus) is involved in executive function [5]. Normal performance of typical cognitive frontal lobe tasks, such as the Wisconsin Card Sorting Task or the Tower of London planning task, depends upon several frontal executive functions including working memory, attention, planning, and cognitive flexibility, all of them pertaining to this frontostriatal loop [20–23]. PD subjects off medication have impaired task set-shifting [24, 25], reduced basal ganglia activation during performance of the Tower of London test [26, 27], and show correlations between the degree of impairment on executive tasks and the degree of dopaminergic hypofunction in the caudate nucleus [28, 29]. These alterations are virtually constant in PD and suggest frontal lobe "deafferentation" caused by dopamine depletion in the dorsal caudate nucleus [24, 30]. There is some indication that such a "deafferentation" predicts incident dementia [31]. Interestingly, the direct dopaminergic projection to the prefrontal cortex seems to be hyperactive early in the course of the disease [32, 33], presumably as a compensatory mechanism (Figure 2). Nonetheless, dorsal caudate-dependent tasks are consistently associated with DLPFC hypoactivation [34].

3.2. Clinical Correlates

3.2.1. OFF Dopaminergic Treatment. Clinical manifestations of frontal lobe dysfunction, including poor planning, defects in set-shifting, impaired working memory, and executive dysfunction, are common in PD without dementia [35] and correlate with a PD-related cognitive pattern of altered glucose metabolism [36]. This pattern is characterized by metabolic reductions in frontal areas, and relative metabolic increases, presumably compensatory, in the cerebellum. Fatigue (mental fatigue) can be present in PDFCD stage I (Figures 1 and 2) and may even precede the onset of motor symptoms [6].

3.2.2. ON Dopaminergic Treatment. Dopaminergic treatment induces impulse control disorders (ICDs) in a number of PD subjects as the result of the overactivation of the "complex" frontostriatal limbic loop [37]. Hence, ICDs occur in PDFCD stages I and IIa (Figure 2; see next section for further details). In contrast to the dopaminergic projections to the striatum, the activity of the dopaminergic projection to the frontal cortex is not expected to be substantially altered by dopaminergic treatment, especially when it is overactive, because it lacks dopamine transporter sites and dopamine D2 autoreceptors [38]. In fact, the action of dopamine in the frontal cortex is mostly mediated by dopamine D1 receptors [39]. This might explain some of the clinical differences between levodopa therapy and treatment with direct dopamine agonists. While levodopa-derived dopamine stimulates D1 and D2 receptors, dopamine agonists predominantly stimulate D2 receptors.

4. PDFCD Stage II: The "Complex" Frontostriatal Limbic Loop

4.1. Functional Analysis. In PD, the damage to the dopaminergic projection to the ventral striatum (ventral caudate and nucleus accumbens) is less prominent than the damage to the dopaminergic projection to the dorsal striatum (putamen and dorsal caudate) [1, 12]. Still, ventral regions of the striatum also undergo substantial dopamine depletion (~60% dopamine loss) [1, 13].

Reversal learning tasks, which basically test for balance between "go" and "no-go" signals [40], are used to assess the "complex" frontostriatal limbic loop (OFC/ACC—ventral caudate/nucleus accumbens) [41]. As one would predict according to the regional differences in the degree of striatal dopamine depletion, PD subjects off medication perform much better in reversal learning tasks than in tasks involving the dorsal caudate circuitry [10, 41–43]. Conversely, dopaminergic therapy improves dorsal caudate related tasks and worsens reversal learning tasks [10, 41, 42]. This paradoxical effect of medication is probably due to the "over-dose" of a relatively normal ventral striatum [10, 42–45]. PD subjects tend to avoid negative outcomes when being off medication, and they are sensitive to positive outcomes when being on medication [40]. In other words, dopaminergic therapy favours "go" signals over "no-go" signals.

4.2. Clinical Correlates. Although it is admittedly difficult to functionally separate the two components of the "complex" frontostriatal limbic loop, there is some suggestion that the OFC—ventral caudate circuit modulates social/emotional behaviour and the ACC—nucleus accumbens circuit mediates motivation and integrates cognitive and emotional iterative networks [9]. Consequently, hypoactivation of the limbic loop, specifically the ACC—nucleus accumbens circuit, is expected to lead to apathy. Limbic loop hyperactivation, on the other hand, is expected to lead to impulsive behaviours.

4.2.1. OFF Dopaminergic Treatment. Depression, anxiety, and apathy are common in PD [6, 46, 47]. Apathy still needs a clear definition. Most authors would agree that it refers

to a lack of motivation [48]. In any case, it is increasingly recognized that apathy is not depression, although both disorders share a number of clinical characteristics, including psychomotor retardation, diminished interest, anergy, and lack of insight [49]. The proof of concept for a distinction between apathy and depression came from the observation that non-PD-depressed patients treated with selective serotonin reuptake inhibitors (SSRIs) sometimes develop apathy [50, 51].

Some imaging studies suggest that depression in PD is associated with dopamine depletion in the ventral striatum [52] and hypoactivation of the cingulate cortex [53, 54]. However, these results may need to be reassessed in view of the increasing awareness of a distinction between depression and apathy. Recent estimates suggest that apathy is more prevalent than depression in PD [6, 47], suggesting that many patients who are assumed to have depression could have apathy instead. In non-PD patients with depression, the ACC (specifically, its subgenual portion) has been found to be hyperactive, not hypoactive [55–57]. In addition, pathological and neuroimaging observations in Alzheimer's disease, where apathy is a very common phenomenon [47], indicate that there is a correlation between apathy and neurofibrillary tangles burden in the anterior cingulate cortex [58–60]. Likewise, apathy in PD correlates with reduced gray matter in the cingulate cortex [61]. Taken together, these observations suggest that depression corresponds to PDFCD stage IIa (hypofunction of the OFC—ventral caudate circuit), and apathy corresponds to PDFCD stage IIb (hypofunction of the ACC—nucleus accumbens circuit) (Figures 1 and 2). Naturally, PDFCD stage IIb also includes hypofunction of the OFC—ventral caudate circuit, which explains why depression and apathy occur sequentially and share several clinical characteristics.

Depression is sometimes a premotor manifestation of PD but more often appears after motor symptom onset [6, 46]. The underlying neurochemical bases may differ in both scenarios. Depression occurring during the pre-motor phase of the disease probably reflects Lewy pathology in raphe nuclei and locus coeruleus, originating serotonergic and noradrenergic abnormalities [16]. Accordingly, depression preceding PD motor symptoms should respond to conventional antidepressants, including SSRIs. Nonetheless, recent neuroimaging studies have challenged this concept by showing preserved serotonin transporter binding in the novo PD subjects [62]. The neurochemical basis of premotor depression remains, therefore, unclear; dopamine dysfunction could play a role. Depression occurring at later stages, on the other hand, is likely related to dopamine depletion in the ventral caudate (PDFCD stage IIa; Figure 2). In this case, treatment is problematic. Many antidepressants, particularly SSRIs, have failed to demonstrate efficacy in PD [63, 64]. In fact, SSRIs can paradoxically precipitate apathy. Neuroimaging studies provide some clues to explain this phenomenon. In non-PD subjects with major depression, antidepressants correct ACC overactivity and there is a correlation between the degree of relative ACC overactivity at baseline and the response to antidepressants [55]. In PD, treatment with SSRIs can lead to apathy by decreasing the activity of the ACC—nucleus accumbens circuit (i.e., SSRI-related functional transition from stage IIa to stage IIb).

Anxiety typically occurs during the motor phase of PD [6, 46]. Although other neurotransmitters are in all likelihood responsible for anxiety during the pre-motor phase of the disease, dopamine depletion in the ventral striatum seems to play a major role once the motor symptoms are established. Thus, the severity of anxiety is inversely correlated with dopamine/noradrenaline transporter binding in caudate, ventral striatum, and amygdala [52]. Animal experiments indicate that stress is associated with decreased dopamine release in the nucleus accumbens and increased dopamine release in the medial prefrontal cortex [65]. This observation suggests that anxiety occurs when the ACC—nucleus accumbens circuit is hypoactive and the direct dopaminergic projection to the frontal cortex is still functionally preserved (PDFCD stage IIb; Figure 2). However, PD subjects on dopaminergic therapy often present with a combination of depression and anxiety during the OFF periods, suggesting a connection between anxiety and PDFCD stage IIa. PD-related functional or pathological alterations in the amygdala [66], a limbic structure known to play an important role in anxiety disorders [67], could ultimately determine whether anxiety occurs in PDFCD stage IIa or stage IIb.

Apathy in PD is proposed to be associated with hypofunction of the ACC—nucleus accumbens circuit (PDFCD stage IIb; Figure 2). A recent study reported apathy in 23% of drug-naïve PD subjects [68], indicating that the limbic loop can be dysfunctional early in the course of the disease. At later stages, when PD subjects develop a combination of striatal and frontal dopamine depletion (PDFCD stage III), apathy is expected to become more prevalent and severe, with even further progression in more advanced PD, with the development of frontal Lewy body pathology [16, 19]. In this context, subjects with frontotemporal dementia have the highest prevalence rates of apathy across disorders with frontal dysfunction [47].

Pain is a nonmotor manifestation of PD known to be influenced by dopaminergic treatment [7, 69]. The PDFCD model suggests that pain (central pain) is related to dopamine depletion in the ventral striatum, specifically in the nucleus accumbens (PDFCD stage IIb; Figure 2). In support of this view, there is experimental evidence suggesting that the nucleus accumbens is involved in a dopamine-opioid network that modulates pain transmission [70, 71]. Pain is sometimes directly related to poor motor performance (dystonic pain) [7], reflecting dopamine depletion in the putamen.

It has already been mentioned that fatigue (mental fatigue) can be an early symptom of PD (PDFCD stage I) [6, 72]. More often, however, it is associated with depression and reduced motivation [6, 73], signalling PDFCD stages IIa and IIb, and possibly stage III as well. Serotonergic dysfunction may contribute to fatigue [74].

4.2.2. ON Dopaminergic Treatment. Remarkably, the PDFCD model suggests that depression can be present during ON periods in stages IIa and IIb (Figure 2),

explaining a relatively common clinical observation (i.e., PD subjects who are depressed off and on medication).

Clinical studies suggest that some 10% of PD subjects treated with dopaminergic medications develop ICDs, including pathological gambling, compulsive shopping, compulsive eating, hypersexuality, and even addictive behaviours [75, 76]. The PDFCD model suggests that ICDs are due to treatment-related hyperactivations of the ACC—nucleus accumbens circuit, and should therefore occur in stages I and IIa (Figure 2). Experimental observations support this notion [77–79]. PD subjects with the so-called "dopamine dysregulation syndrome" (i.e., subjects with abusive use of anti-PD medication) release large amounts of dopamine in the ventral striatum after levodopa administration [77]. It is known that the release of dopamine in the nucleus accumbens has rewarding effects [80], which would lead to the perpetuation of impulsive behaviours. Naturally, dopamine-related increases in the dopaminergic tone of the ventral striatum are expected to cause hyperactivation of ACC and OFC. In keeping with the PDFCD model, imaging studies in non-PD subjects with obsessive-compulsive disorder have shown decreased dopamine D2 binding—highly suggestive of increased dopamine levels—in the ventral striatum, and hyperactivation of OFC and ACC [81–84]. As the caudate nucleus modulates abnormal behaviours [5, 85], it could be tentatively argued that primarily compulsive behaviours (e.g., punding) might be more common in PDFCD stage I, and primarily reward-related ICDs (e.g., pathological gambling) might be more common in PDFCD stage IIa. In this context, ICDs in PD are associated with depression, anxiety, and obsessive-compulsive symptoms [86]. Clinical studies suggest that young PD subjects are at high risk of developing ICDs [76], perhaps in relation to age-dependent dopamine release dynamics [87]. Younger PD subjects release more dopamine, and at a faster rate, than older PD subjects.

Treatment-related visual hallucinations sometimes herald the development of dementia [6]. The PDFCD model suggests that, by the time the first hallucinations appear, all the dopamine-dependent frontostriatal loops are already dysfunctional (hypoactive) in the OFF state, whereas the dopaminergic projection to the frontal cortex is still preserved (PDFCD stage IIb; Figure 2). In this situation, frontal dopamine levels are expected to increase in response to dopaminergic treatment (ON state), possibly explaining why visual hallucinations are associated with relative frontal hypermetabolism [88]. Nonetheless, visual hallucinations in PD are also linked to hypometabolism in occipitotemporoparietal regions [89].

5. PDFCD Stage III: The Dopaminergic Projection to the Frontal Cortex

The damage to the direct dopaminergic projection to the frontal cortex signals the beginning of dementia [17, 18]. At this stage (PDFCD stage III; Figure 2), the patient begins to oscillate between dementia in the OFF state and psychosis in the ON state, a cycle that becomes more pronounced and fully established in more advanced PD, with the development of cortical Lewy body pathology. Other times, the patient remains apathetic during both OFF and ON periods.

In addition to striatal and frontal dopamine depletion, other neurotransmitters are also involved in PD dementia. Indeed, cortical cholinergic dysfunction can be even more severe in PD subjects with dementia than in patients with Alzheimer's disease [90, 91]. In advanced PD, cortical pathology—not only Lewy bodies but also neurofibrillary tangles and amyloid deposits—becomes a major contributing factor. Thus, in vivo PET studies have found comparable levels of cortical amyloid binding in patients with dementia with Lewy bodies and patients with Alzheimer's disease [92, 93].

6. Conclusions

The PDFCD model provides a systematic assessment of cognitive and behavioural symptoms, which may help clinicians optimize therapeutic strategies. It also provides a framework for hypothesis testing. For example, in prospective studies, apathy should not appear before ICDs in most patients. The model has a number of strengths and limitations. Among its strengths, it is simple and fits well clinical observations. For example, it explains why depression can be present during both OFF and ON periods, why depression and apathy are different disorders, and why some patients oscillate between apathy and depression or between dementia and psychosis. The combination of ON-period depression and impulsivity (PDFCD stage IIa) is relevant to explain why some PD subjects treated with subthalamic stimulation attempt suicide [94, 95]. Among its limitations, the model is in part *ad hoc* and does not contemplate region-specific assessments of the direct dopaminergic projection to the frontal cortex. In the early stages of PD, for example, cortical dopamine upregulation might only involve the DLPFC [32, 33]. There is evidence to suggest that the dopaminergic projection to the frontal cortex has limited capability for adaptation in response to dopaminergic treatment, particularly levodopa, due to its lack of dopamine transporter sites and dopamine D2 autoreceptors [38]. Still, treatment-related psychosis occurring in PDFCD stage III could be associated with relative dopaminergic hyperactivity in the frontal cortex. In other words, frontal cortex "overdose" may still be possible in later stages causing psychosis. Finally, the model assumes that dopamine-dependent frontostriatal functioning follows an inverted U-shaped dose-response curve. Whereas this type of dopamine response seems to operate in the frontal cortex [96], it might not necessarily occur in the striatum. Additional model refinements are certainly needed, including a better definition of stages IIa and IIb. To reach this goal, we need to develop better tools to reliably distinguish between depression and apathy [97] and reliably measure apathy and fatigue [98, 99].

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Research Article

Adenosine A_{2A} Receptor Antagonists Do Not Disrupt Rodent Prepulse Inhibition: An Improved Side Effect Profile in the Treatment of Parkinson's Disease

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Parkinson's disease (PD) is characterized by loss of dopaminergic neurons in the substantia nigra. Current treatments for PD focus on dopaminergic therapies, including L-dopa and dopamine receptor agonists. However, these treatments induce neuropsychiatric side effects. Psychosis, characterized by delusions and hallucinations, is one of the most serious such side effects. Adenosine A_{2A} receptor antagonism is a nondopaminergic treatment for PD with clinical and preclinical efficacy. The present studies assessed A_{2A} antagonists SCH 412348 and istradefylline in rodent prepulse inhibition (PPI), a model of psychosis. Dopamine receptor agonists pramipexole (0.3–3 mg/kg), pergolide (0.3–3 mg/kg), and apomorphine (0.3–3 mg/kg) significantly disrupted PPI; ropinirole (1–30 mg/kg) had no effect; L-dopa (100–300 mg/kg) disrupted rat but not mouse PPI. SCH 412348 (0.3–3 mg/kg) did not disrupt rodent PPI; istradefylline (0.1–1 mg/kg) marginally disrupted mouse but not rat PPI. These results suggest that A_{2A} antagonists, unlike dopamine agonists, have an improved neuropsychiatric side effect profile.

1. Introduction

Parkinson's disease (PD) is characterized by a progressive loss of dopaminergic neurons in the substantia nigra region of the basal ganglia, which results in movement-related symptoms. Current treatment for PD includes dopamine replacement therapy in the form of L-dopa, a precursor to dopamine (DA) in its synthesis pathway that has been the gold standard of care for decades. More recently, DA receptor agonists, such as pramipexole, pergolide, and ropinirole, have become more commonly prescribed for the treatment of PD.

PD is primarily associated with motor symptoms, but nonmotor neuropsychiatric symptoms have garnered recent attention as serious complications that negatively impact quality of life [1, 2]. Psychosis, mostly in the form of visual hallucinations and sometimes paranoid delusions, is a troubling neuropsychiatric symptom in PD patients. Treatment with dopaminergic medication is a risk factor for developing psychosis. Up to 40% of PD patients treated with dopaminergic agents experience psychotic symptoms, of which the most common manifestations are visual hallucinations [3, 4], whereas less than 10% of untreated PD patients experience psychotic symptoms [5]. Among the antiparkinsonian medications, studies have shown that DA receptor agonists are more likely to induce psychoses than L-dopa [5–7]. First-line treatment for psychosis in PD is typically dose reduction of dopaminergic agents. Second-line treatment is administration of atypical antipsychotics, particularly clozapine and quetiapine [8]. However, these drugs carry the risk of worsening the motor symptoms of PD either by counteracting the dopaminergic treatment effects or inducing extrapyramidal side effects [9]. Better treatment options for PD without the associated psychosis liability would be extremely beneficial.

Given the clinical link between dopaminergic therapies and psychoses, preclinical models of psychosis that are translatable to humans are necessary to predict the psychosis risk of novel PD medications. Prepulse inhibition (PPI) of startle

is a preclinical model of sensory gating that we used in the current studies to evaluate this risk for A_{2A} receptor antagonists. Typically, PPI deficits are associated with neuropsychiatric disorders such as schizophrenia. DA receptor agonists disrupt PPI in rats and humans [10–12], which demonstrates the cross-species reliability of the PPI model. These findings also provide evidence that PPI disruptions can be used to predict neuropsychiatric side effects of PD medications.

Adenosine A_{2A} receptor antagonism has recently emerged as a potential novel nondopaminergic treatment for PD. A_{2A} receptors are abundant in the GABAergic neurons of the indirect pathway of the basal ganglia [13]. The location of these receptors suggests that they are potent neuromodulators and may regulate excitatory input to the striatum, which is an important target for PD treatment due to its involvement in the control of voluntary movements [14]. A_{2A} receptor antagonism has proven beneficial in clinical trials. In a recent phase II clinical trial, the A_{2A} antagonist preladenant was found to decrease off time and motor fluctuations in patients with PD receiving L-dopa [15].

A_{2A} receptor antagonists have also demonstrated efficacy in animal models of PD. The A_{2A} receptor antagonist istradefylline (KW-6002) increased locomotor activity in MPTP-treated mice and decreased mouse catalepsy induced by haloperidol or reserpine [16]. Of particular interest to the present studies is SCH 412348, which is a novel and potent A_{2A} antagonist that displays high selectivity (>1000-fold) over all other adenosine receptor subtypes (K_i = 0.6 nM) [17]. SCH 412348 (0.1–1.0 mg/kg) has been shown to potentiate L-dopa-induced rotations in 6-OHDA-lesioned rats and reverse rat haloperidol-induced catalepsy, two rodent models predictive of antiparkinsonian efficacy [17].

The purpose of the current research was to evaluate any potential psychosis liability of A_{2A} antagonists. SCH 412348 and istradefylline were assessed in both rat and mouse PPI and compared to current dopamine-based PD therapies (pra-mipexole, pergolide, ropinirole, L-dopa, and apomorphine). Doses tested in PPI were based on efficacy in rat haloperidol-induced catalepsy.

2. Materials and Methods

2.1. Animals. Male CD rats weighing 180–220 g and 250–450 g were used in catalepsy and PPI studies, respectively. Male C57BL/6 mice (20–25 g) were used in mouse PPI studies. Animals were purchased from Charles River Laboratories (Kingston, NY, USA). Animals were group-housed with food and water available ad libitum. Studies were conducted during the light phase of a 12 h light/dark cycle under standard laboratory conditions (constant temperature and humidity). Animal care and testing procedures were conducted in conformity with the Merck Institutional Animal Care and Use Committee, and in compliance with the "Guide for the Care and Use of Laboratory Animals" (National Research Council, 1996) and the Animal Welfare Act.

2.2. Drugs. Haloperidol, pergolide mesylate, ropinirole hydrochloride, L-dopa, benserazide, and apomorphine were obtained from Sigma-Aldrich (St. Louis, Mo, USA). Pramipexole·2HCl was purchased from Tecoland Corporation (Edison, NJ, USA). For catalepsy studies, haloperidol was prepared with distilled water and brought to a pH of 5-6 with 0.1 N HCl and 0.1 M NaOH. A dose of 1 mg/kg was administered SC 30 min prior to catalepsy testing. SCH 412348 ([7-[2-[4-2,4-difluorophenyl]-1-piperazinyl]ethyl]-2-(2-furanyl)-7H-pyrazolo[4,3-e][1, 2, 4]triazolo[1,5-c]pyrimidin-5-amine) and istradefylline [(E)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methyl-3,7-dihydro-1H-purine-2,6-dione] were synthesized by the Department of Chemical Research at Merck Research Laboratories. SCH 412348 was prepared in 0.4% methylcellulose and administered orally 60 min prior to behavioral testing. Istradefylline was dissolved in 5% Tween 80 in saline and administered orally 60 min prior to behavioral testing. Pramipexole was dissolved in saline and injected sc. 30 min prior to behavioral testing. Pergolide was prepared in saline and dosed ip. 10 min prior to testing. Ropinirole was dissolved in saline and injected ip. 60 min prior to testing. L-dopa was prepared in saline and administered ip. 60 min prior to catalepsy or PPI testing. Twenty min prior to L-dopa, benserazide dissolved in saline was injected ip. (2 : 1 ratio of L-dopa to benserazide) to prevent peripheral decarboxylation of L-dopa. Apomorphine solution in 0.1% ascorbic acid was administered sc. 5 min prior to PPI testing. In rats, dose volume for oral administration was 5 mL/kg, while dose volume for both sc. and ip. administration was 1 mL/kg. Dose volume for all routes of administration in mice was 10 mL/kg.

2.3. Haloperidol-Induced Catalepsy Procedure. The catalepsy procedure followed that described by Hodgson et al., in 2009 [17]. Catalepsy was measured using an angled wire mesh screen (60° angle, 59 cm (W) × 24 cm (D) × 56.0 cm (H); mesh 5 mm^2). The duration of catalepsy was scored by an experimenter using a hand-held timer. Rats were first injected with haloperidol to induce catalepsy. Thirty minutes later, each rat was placed on the wire mesh screen with its head facing upward and forelimbs and hindlimbs extended. To prescreen the rats to ensure they were responsive to haloperidol, they were given two trials to demonstrate catalepsy (operationally defined as remaining still without lifting a paw from the wire mesh) for 120 sec to meet study inclusion threshold. Haloperidol was not injected a second time for the second trial. Rats that met the criterion (roughly 85% of the rats tested) on at least one of the two trials were injected with the drug of interest and tested for catalepsy after the appropriate pretreatment time. The latency to move a paw was the dependent measure in the catalepsy studies, with all trials truncated at 120 sec. Studies were conducted using a between-subjects design.

2.4. Prepulse Inhibition Procedure. Ventilated and lighted startle chambers (SR-LAB; San Diego Instruments, San Diego, Calif, USA) were utilized for all PPI experiments. Each chamber (33 × 33 × 46 cm) was equipped with a loudspeaker (acoustic source) and a Plexiglas cylindrical animal enclosure (internal diameter: 8.8 cm for rat, 3.8 cm for

mouse) mounted on a Plexiglas base. Startle responses were transduced by a piezoelectric accelerometer mounted below the cylinder. The loudspeaker was positioned above the cylinder and produced the mixed frequency stimuli (background noise, prepulse and pulse stimuli).

Test sessions began with a 5 min acclimation period, during which a background noise was presented in the absence of any startle stimuli. The animals were then subjected to a series of acoustic startle trials. For mouse PPI, the animals received six trial types: no stimulus, startle alone (130 dB, 40 ms), highest prepulse alone (20 ms), and three different prepulses (5 dB, 10 dB, and 15 dB, 20 ms) preceding a startle stimulus by 100 ms. Each trial type was presented in a pseudorandom order with 12 presentations of each, in addition to an initial single pulse alone trial which began the test session. This initial pulse trial was not used in data analysis. The intertrial interval averaged 18 s (10–25 s range). For rat PPI, a total of 41 trials were presented. They consisted of five trial types: no stimulus, startle alone (120 dB, 40 ms), and 3 prepulse stimuli (5, 10, and 15 dB above 65 dB background, 20 ms), each preceding the startle stimulus by 100 ms. Each trial type was presented in a pseudorandom order with 8 presentations of each in addition to an initial single pulse alone trial, which was not used for data analysis. The average intertrial interval was 20 s (15–25 s range). PPI data are expressed as an average of the percent inhibition of startle produced by the 5, 10, and 15 dB prepulse trials. Mean startle magnitude was calculated based on the startle alone trials. All animals were initially subjected to a baseline testing day without pharmacological manipulation in order to create groups with equivalent mean baseline levels of startle and PPI. All studies were conducted using a between-subjects design.

2.5. Statistical Analysis. All data are expressed as means ± the standard error of the mean (SEM). All studies were analyzed using one-way ANOVAs. Dunnett's tests were used to determine individual dose groups with significant reductions in time cataleptic compared to the haloperidol + vehicle group for catalepsy studies or individual dose groups with significant reductions in percent PPI or startle compared to the vehicle group in PPI studies. Significance was defined as $P < 0.05$.

3. Results

3.1. Haloperidol-Induced Catalepsy. Figure 1 shows treatment effects on rat haloperidol-induced catalepsy. The A_{2A} antagonists SCH 412348 (Figure 1(a)) and istradefylline (Figure 1(b)) significantly reversed rat haloperidol-induced catalepsy (SCH 412348: $F(5, 42) = 15.57$, $P < 0.01$; istradefylline: $F(5, 42) = 9.20$, $P < 0.01$), with the 0.3, 1, and 3 mg/kg groups and the 0.3 and 1 mg/kg groups, respectively, spending significantly less time cataleptic than the vehicle + haloperidol group. The DA receptor agonists pramipexole, pergolide and ropinirole also reduced haloperidol-induced catalepsy in rats. Pramipexole effects ($F(6, 35) = 7.57$, $P < 0.01$) were significantly different from vehicle at 0.1, 0.3, 1, and 3 mg/kg (Figure 1(c)), while pergolide ($F(5, 42) = 19.98$, $P < 0.01$) showed significant effects compared to vehicle at doses of 3 and 10 mg/kg (Figure 1(d)). Ropinirole reduced time cataleptic ($F(5, 30) = 11.42$, $P < 0.01$) at 10 mg/kg, whereas 1 and 3 mg/kg showed marginal significance ($P = 0.06$) compared to vehicle + haloperidol treatment (Figure 1(e)). L-dopa significantly reduced haloperidol-induced catalepsy ($F(5, 50) = 7.13$, $P < 0.01$) at 100 mg/kg, whereas 300 mg/kg approached significance ($P = 0.06$) compared to vehicle + haloperidol treatment (Figure 1(f)).

3.2. Rat PPI. Figure 2 (left graphs) shows treatment effects on rat PPI, and Table 1 shows treatment effects on rat startle magnitude. The A_{2A} antagonists SCH 412348 (Figure 2(a)) and istradefylline (Figure 2(b)) did not impair rat PPI (SCH 412348: $F(3, 28) = 0.57$, $P > 0.05$; istradefylline: $F(3, 28) = 1.18$, $P > 0.05$) or startle magnitude (SCH 412348: $F(3, 28) = 0.31$, $P > 0.05$; istradefylline: $F(3, 28) = 0.20$, $P > 0.05$) at any doses tested. Pramipexole (Figure 2(c)) significantly reduced PPI at all doses tested (0.3, 1, and 3 mg/kg) ($F(3, 60) = 4.47$, $P < 0.01$) but also significantly reduced startle magnitude at all doses tested ($F(3, 60) = 5.24$, $P < 0.01$) compared to vehicle, which is consistent with previous findings [11]. Pergolide (Figure 2(d)) impaired PPI at 0.3 and 3 mg/kg ($F(3, 60) = 5.64$, $P < 0.01$) but did not affect startle ($F(3, 60) = 1.29$, $P > 0.05$). Ropinirole (Figure 2(e)) did not impair PPI in rats ($F(4, 32) = 1.16$, $P > 0.05$) but reduced startle magnitude at 3 and 30 mg/kg ($F(4, 32) = 4.61$, $P < 0.01$). For L-dopa (Figure 2(f)), a one-way ANOVA revealed only a marginally significant effect on PPI overall ($F(4, 35) = 2.46$, $P = 0.06$). The two highest doses of L-dopa (100 and 300 mg/kg) significantly disrupted PPI. Startle was not affected by treatment with L-dopa ($F(4, 35) = 0.23$, $P > 0.05$). Apomorphine (Figure 2(g)) significantly reduced PPI in rats ($F(4, 75) = 5.58$, $P < 0.01$) at all doses tested (0.3, 0.5, 0.65, and 0.8 mg/kg) but had no effect on startle ($F(4, 75) = 0.76$, $P > 0.05$).

3.3. Mouse PPI. Figure 2 (right graphs) shows treatment effects on mouse PPI, and Table 2 shows treatment effects on mouse startle magnitude. SCH 412348 (Figure 2(a)) did not significantly decrease PPI or startle in mice (PPI: $F(3, 36) = 0.74$, $P > 0.05$; startle: $F(3, 36) = 0.14$, $P > 0.05$). Istradefylline (Figure 2(b)) approached overall significance in reducing mouse PPI ($F(3, 36) = 2.83$, $P = 0.05$). Istradefylline (1 mg/kg) significantly reduced PPI compared to vehicle. Startle was not affected by istradefylline at any dose ($F(3, 36) = 1.26$, $P > 0.05$). Pramipexole (Figure 2(c)) significantly reduced PPI in mice only at 1.0 mg/kg ($F(3, 44) = 2.91$, $P < 0.05$). Unlike its effects on rat startle magnitude, pramipexole did not significantly reduce mouse startle ($F(3, 44) = 2.53$, $P > 0.05$). Pergolide (Figure 2(d)) significantly reduced mouse PPI and startle at 3 mg/kg (PPI: $F(4, 43) = 3.40$, $P < 0.05$; startle: $F(4, 43) = 3.63$, $P < 0.05$). Ropinirole (Figure 2(e)) did not significantly reduce mouse PPI ($F(3, 36) = 2.09$, $P > 0.05$) or startle magnitude ($F(3, 36) = 0.05$, $P > 0.05$) at any dose tested. For L-dopa (Figure 2(f)), there was no significant main effect of dose on PPI ($F(4, 42) = 1.01$,

Table 1: Mean startle magnitude ± SEM in rat prepulse inhibition (*$P < 0.05$ versus vehicle).

Drug	Dose (mg/kg)	Startle
SCH 412348	Veh.	193.3 ± 46.6
	0.3	223.4 ± 59.5
	1.0	166.0 ± 20.2
	3.0	213.0 ± 46.3
Istradefylline	Veh.	196.5 ± 50.8
	0.1	163.7 ± 26.7
	0.3	161.5 ± 23.3
	1.0	175.0 ± 36.9
Pramipexole	Veh.	229.5 ± 32.1
	0.3	121.4 ± 14.4*
	1.0	134.7 ± 32.0*
	3.0	101.6 ± 14.2*
Pergolide	Veh.	139.9 ± 20.7
	0.3	104.9 ± 27.1
	1.0	111.0 ± 19.1
	3.0	84.0 ± 11.1
Ropinirole	Veh.	250.2 ± 49.7
	1.0	218.8 ± 33.7
	3.0	73.0 ± 17.6*
	10.0	166.6 ± 26.7
	30.0	111.4 ± 22.1*
L-dopa	Veh.	228.7 ± 124.7
	10	183.5 ± 31.0
	30	269.8 ± 63.7
	100	239.0 ± 45.1
	300	197.2 ± 49.8
Apomorphine	Veh.	303.2 ± 46.3
	0.3	323.5 ± 44.3
	0.5	456.3 ± 140.0
	0.65	468.1 ± 76.2
	0.8	355.2 ± 79.6

Table 2: Mean startle magnitude ± SEM in mouse prepulse inhibition (*$P < 0.05$ versus vehicle).

Drug	Dose (mg/kg)	Startle
SCH 412348	Veh.	129.0 ± 17.8
	0.3	144.6 ± 17.8
	1.0	140.5 ± 20.7
	3.0	142.6 ± 12.9
Istradefylline	Veh.	125.9 ± 22.3
	0.1	104.9 ± 17.3
	0.3	110.9 ± 19.0
	1.0	75.9 ± 10.7
Pramipexole	Veh.	95.6 ± 8.7
	0.3	103.1 ± 13.2
	1.0	76.3 ± 8.5
	3.0	69.5 ± 10.5
Pergolide	Veh.	135.2 ± 23.5
	0.1	149.9 ± 12.3
	0.3	116.9 ± 17.6
	1.0	100.5 ± 15.1
	3.0	62.7 ± 10.9*
Ropinirole	Veh.	135.9 ± 19.7
	3.0	134.1 ± 15.2
	10.0	143.3 ± 15.6
	30.0	140.6 ± 18.0
L-dopa	Veh.	130.5 ± 20.9
	10.0	135.0 ± 16.4
	30.0	96.8 ± 14.4
	100.0	69.0 ± 5.8*
	300.0	50.7 ± 9.6*
Apomorphine	Veh.	149.9 ± 26.4
	0.3	93.1 ± 15.9
	1.0	90.6 ± 15.2
	3.0	94.7 ± 13.5

$P > 0.05$). However, startle was significantly reduced by 100 and 300 mg/kg of L-dopa ($F(4, 42) = 5.48$, $P < 0.01$). Apomorphine (Figure 2(g)) significantly reduced mouse PPI at all doses tested (0.3, 1, and 3 mg/kg) ($F(3, 43) = 5.96$, $P < 0.01$) but did not affect startle magnitude ($F(3, 43) = 2.58$, $P > 0.05$).

4. Discussion

A_{2A} receptor antagonism has received considerable recent attention as an alternative treatment for the motor symptoms of PD [18, 19]. A_{2A} receptor antagonists have proven to be efficacious in animal models of PD and in clinical studies. Because they represent a nondopaminergic approach to the treatment of PD, we hypothesized that A_{2A} receptor antagonists will avoid neuropsychiatric side effects associated with dopaminergic therapies, including psychosis. The findings of the present studies are consistent with this hypotheisis.

PPI can be measured in humans, rats, mice, and other mammals and is deficient in pathological or drug-induced psychotic states. In the current studies, pramipexole, pergolide, and apomorphine disrupted PPI in both rat and mouse. These results are consistent with previous findings in rats [10, 11, 20]. Moreover, the disruptive effects occurred at doses that were efficacious in rat haloperidol-induced catalepsy, a rodent model of PD. Although Swerdlow et al. [10] found thatz ropinirole (3–6 mg/kg) induced deficits in rat PPI, ropinirole did not impair PPI in the present studies, even when tested up to 30 mg/kg in the rat and mouse. The different effects on PPI between ropinirole and other DA receptor agonists are consistent with their clinical profiles. PD patients treated with pramipexole have a significantly higher risk of experiencing hallucinations than patients treated with ropinirole [21]. In addition, ropinirole is less likely to induce psychosis when used as monotherapy for PD than when administered adjunctively with other DA receptor agonists [22]. Like pramipexole and pergolide, ropinirole is a potent D_2 and D_3 receptor agonist that favors the D_3 receptor, as does the

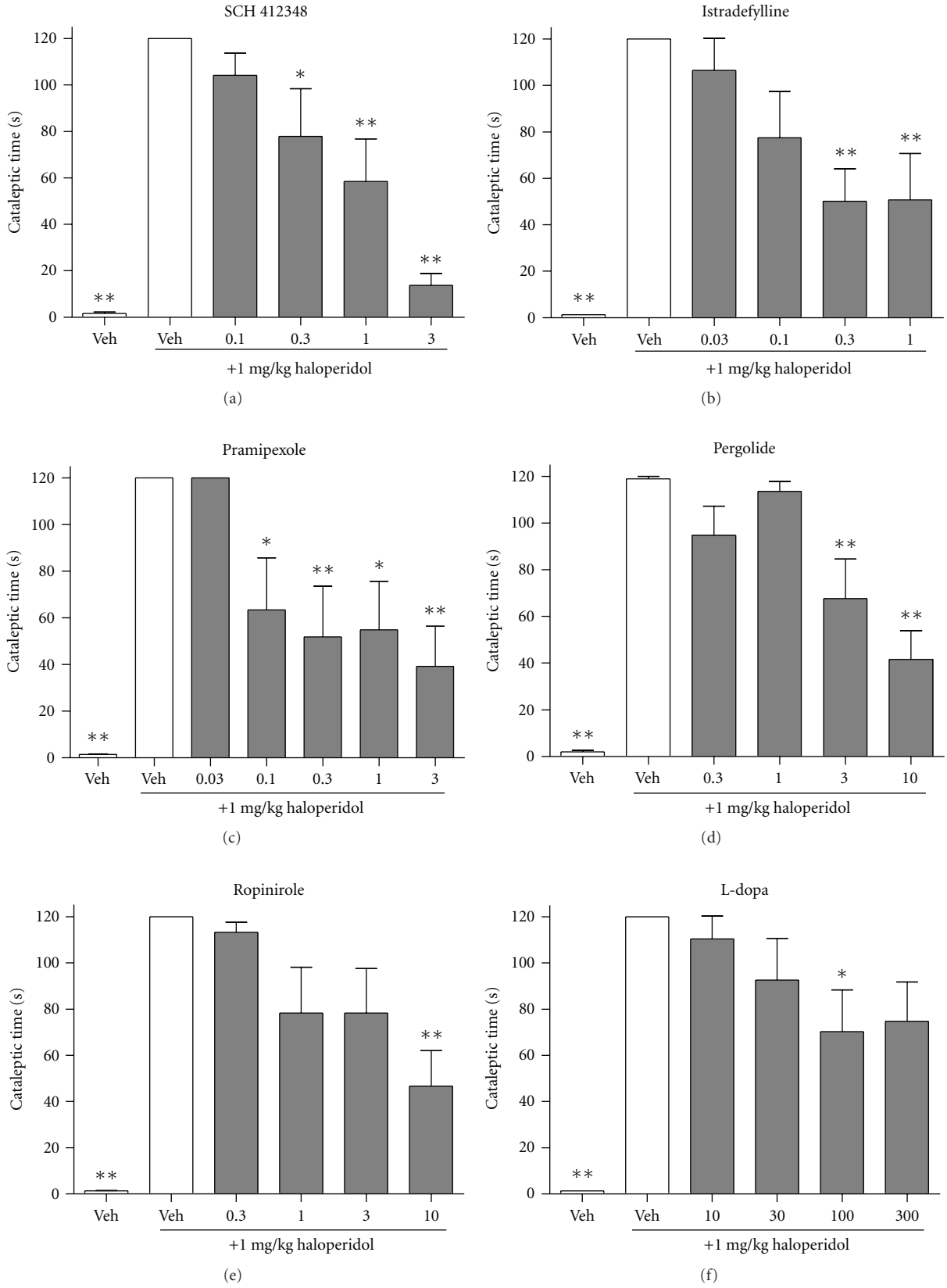

Figure 1: Efficacy of SCH 412348 (a), istradefylline (b), pramipexole (c), pergolide (d), ropinirole (e), and L-dopa (f) to reduce catalepsy induced with 1 mg/kg haloperidol in rats. Data represent mean time cataleptic ± SEM and were analyzed by one-way ANOVAs with Dunnett's tests ($^{*}P < 0.05$; $^{**}P < 0.01$ versus vehicle + haloperidol treatment).

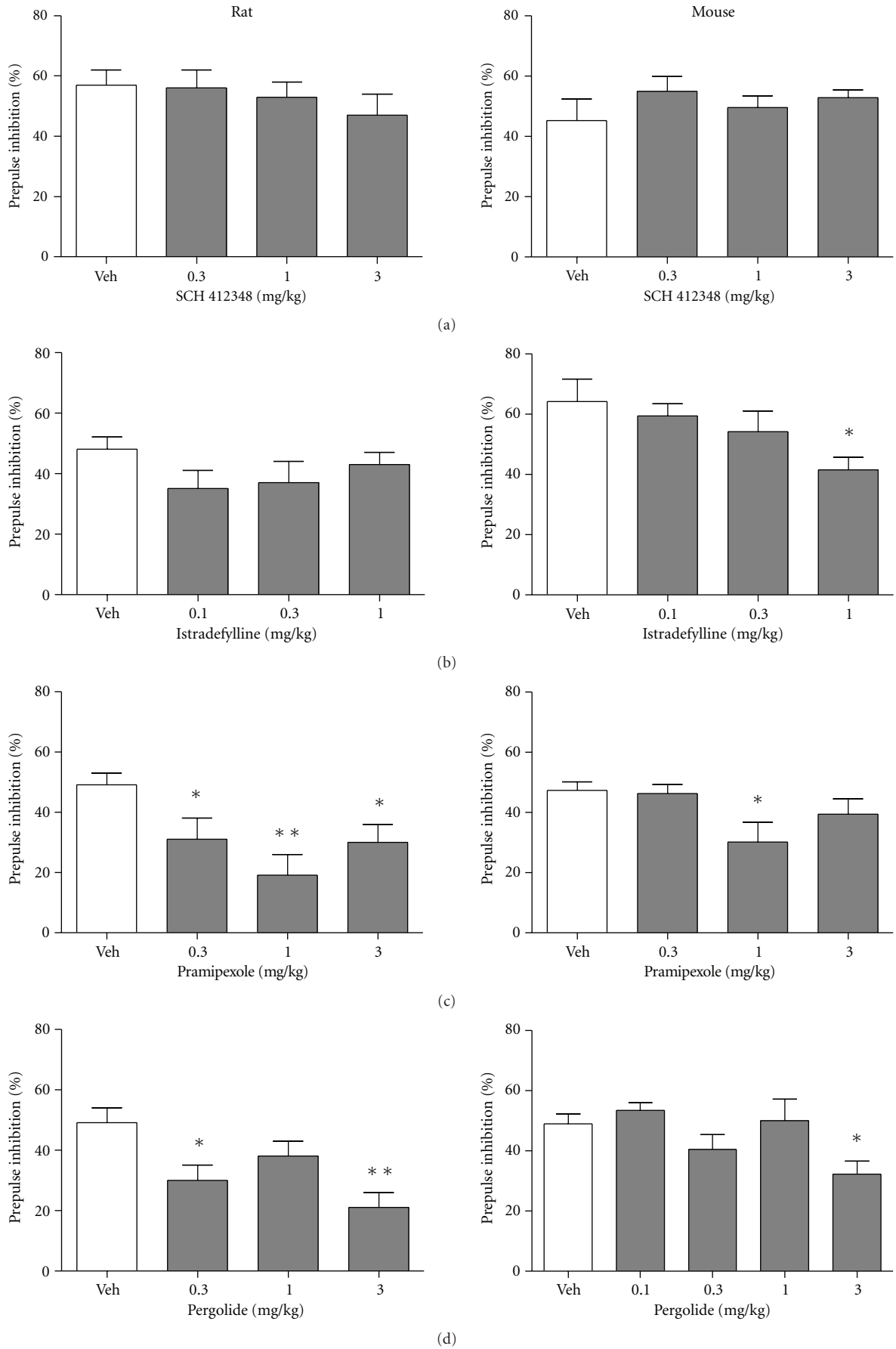

Figure 2: Continued.

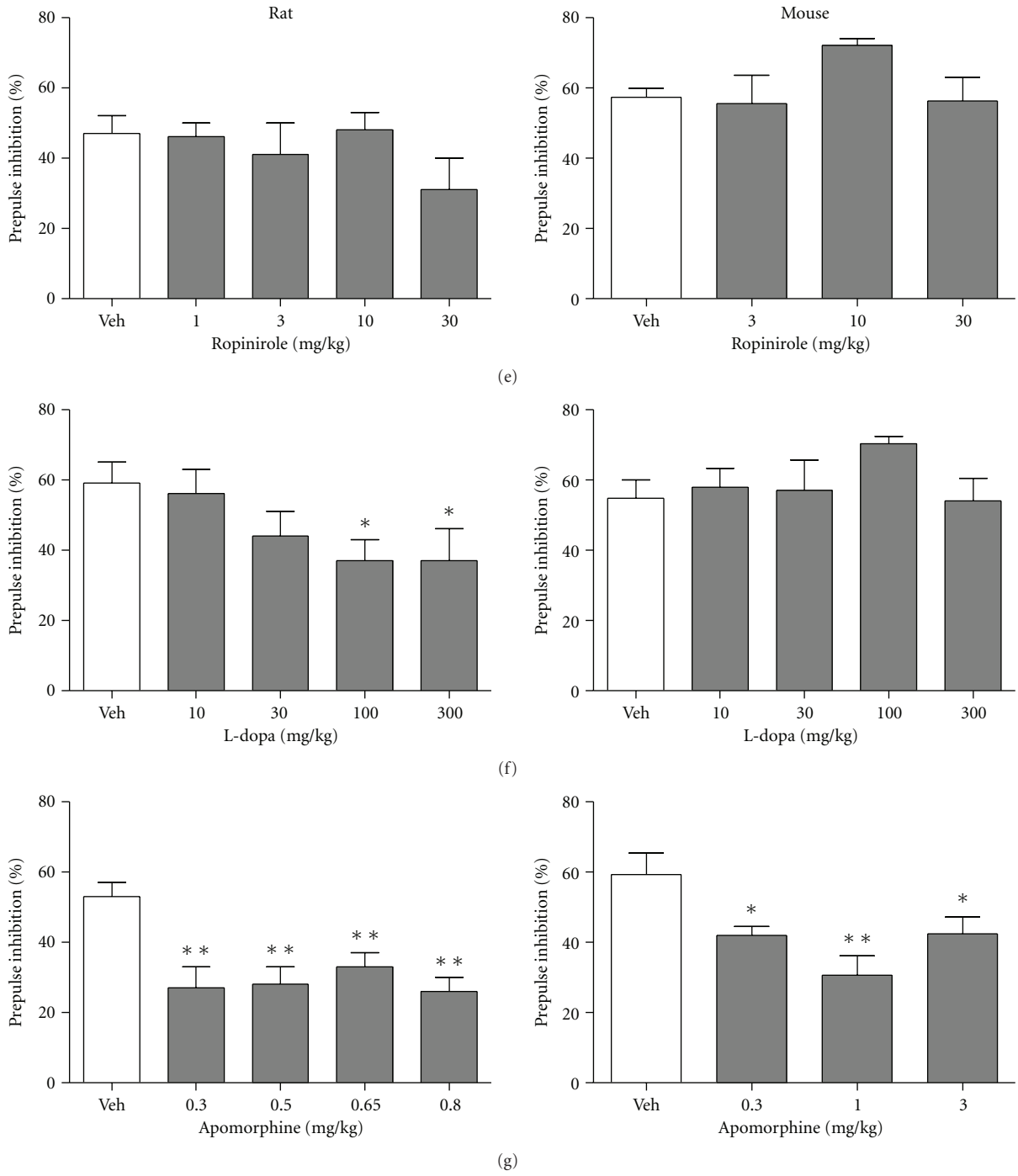

Figure 2: Effects of SCH 412348 (a), istradefylline (b), pramipexole (c), pergolide (d), ropinirole (e), L-dopa (f), and apomorphine (g) on rat (left) or mouse (right) prepulse inhibition. Data represent mean % PPI ± SEM and were analyzed by one-way ANOVAs with Dunnett's tests ($^*P < 0.05$; $^{**}P < 0.01$ versus vehicle treatment).

major metabolite of ropinirole [23]. As such, the difference between ropinirole's psychosis liability as compared to other DA receptor agonists is not clearly understood.

We found that L-dopa produced a marginal disruption of rat PPI but did not disrupt mouse PPI. There are conflicting reports about the relative psychosis liability of L-dopa versus DA receptor agonists. Some findings indicate that L-dopa has similar potential to DA receptor agonists to elicit psychosis [24], whereas other studies suggest that DA agonists are more likely to induce psychosis than L-dopa [5–7].

The clear lack of PPI disruption with SCH 412348 is interesting considering that the efficacy of both DA receptor agonists and A_{2A} antagonists is hypothesized to be mediated by similar effects at the second messenger level. The receptors

are colocalized on neurons in the striatopallidal indirect pathway of the basal ganglia. A_{2A} receptor antagonists and D_2 receptor agonists decrease intracellular adenylyl cyclase activation [25]. These pharmacological approaches evoke similar behavioral profiles in rodents and primates. Several findings provide evidence for extrastriatal DA receptor involvement in PPI [26]. It is possible, therefore, that neuropsychiatric side effects associated with DA receptor agonists are, at least partially, mediated by activity outside the striatum. Unlike D_2 receptors, A_{2A} receptors are predominantly localized in the striatum [14], which could explain their benign neuropsychiatric side effect profile.

The distinction between the two approaches may be attributed to different effects on the various DA receptor subtypes. While it is well established that there is a functional A_{2A}-D_2 receptor interaction, the relationship between A_{2A} and D_3 receptors is less well understood [27]. Chang et al. [20] demonstrated that PPI using acoustic startle is highly sensitive to activation of the D_3 receptor. More research is necessary to better understand the pharmacology responsible for the PPI-disruptive effects of agonism at various DA receptor subtypes as well as the difference between selective A_{2A} antagonists and DA receptor agonists reported herein.

Interestingly, istradefylline induced a marginal disruption of mouse PPI at the highest dose tested (1 mg/kg). The dissimilar effects of SCH 412348 and istradefylline in rodent PPI may be due to their relative activity at the adenosine A_1 receptor. Whereas SCH 412348 is greater than 1000-fold selective for the A_{2A} receptor over the A_1 receptor, istradefylline exhibits only 82-fold selectivity [17]. Koch and Hauber [28] found that the nonselective adenosine receptor antagonist, theophylline, potentiated an apomorphine disruption of PPI. This effect was reversed by a selective A_1 receptor agonist but not a selective A_{2A} receptor agonist. Collectively, these data suggest that istradefylline's activity at the A_1 receptor may have contributed to the disruption of PPI observed at the highest dose tested.

Although psychotic symptoms may also occur in PD patients in the absence of pharmacological treatment, it is still uncertain if the pathology of the disease itself predisposes the patients to developing neuropsychiatric symptoms with dopaminergic treatment. Studies have suggested that PD-associated psychosis results from interactions between pharmacological and disease-related factors [29]. Considering that the present studies were performed using healthy animals, future PPI studies using an animal model of PD, such as the MitoPark mouse, which has a gradual degeneration of dopamine cells and a parkinsonian phenotype [30], may help elucidate the contribution of the disease to the neuropsychiatric effects of dopaminergic treatment. Marcellino et al. [31] reported that chronic treatment with an A_{2A} antagonist alleviated the motor deficits of MitoPark mice. Therefore, a comparison of the effects of A_{2A} receptor antagonists to dopamine receptor agonists in the sensory gating PPI model using MitoPark mice would be beneficial in further understanding the potential benefits of A_{2A} receptor antagonism as a treatment for PD without increased risk of developing psychosis.

5. Conclusions

The highly selective A_{2A} receptor antagonist, SCH 412348, did not induce a PPI deficit in either the rat or mouse. Conversely, DA receptor agonists used for the treatment of PD demonstrated disruptive effects in PPI. Istradefylline modestly disrupted rodent PPI, which we attribute to its activity at the adenosine A_1 receptor. Clearly, more work is required to understand the pharmacology of the disruptive effects of different antiparkinsonian agents. Collectively, our data indicate that A_{2A} receptor antagonism is a promising nondopaminergic treatment for PD that may avoid neuropsychiatric side effects provided that the antagonist has sufficient selectivity over the A_1 receptor.

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Research Article

Impact of Anxiety on Quality of Life in Parkinson's Disease

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In Parkinson's disease (PD), both the patient and the health care provider look for ways to preserve the patient's quality of life. Many studies focus on the impact of depression and motor disability on poor life quality but neglect to examine the role of anxiety. We investigated the impact of anxiety and depression on health-related quality of life in PD, using the Parkinson's Disease Quality of Life measure (PDQ-39). Symptoms of anxiety, more than depression, cognitive status, or motor stage, significantly affected quality of life in 38 nondemented patients with mild-to-moderate motor disability. Stepwise regression analyses revealed that anxiety explained 29% of the variance in the PDQ-39 sum score, and depression explained 10% of the variance beyond that accounted for by anxiety. The findings suggest that primary management of anxiety as well as depression may be important to optimizing the quality of life of PD patients.

1. Introduction

Parkinson's disease (PD) is a chronic and progressive neurological condition in which nonmotor disturbances as well as motor deficits significantly impact quality of life. The disease is characterized by motor signs including tremor, rigidity, bradykinesia, and disorders of gait and balance. In addition to the difficulties in motor control, which occur as a result of progressive loss of the dopamine-producing neurons in the substantia nigra and dysfunction of the basal ganglia, PD patients also frequently experience disturbances in mood and cognition. These prevalent and disabling nonmotor symptoms may have a greater impact on the patients' quality of life than do the principal motor features of PD [1–6].

Depression is the most commonly explored mood disorder influencing quality of life in PD and has been found to be the best predictor overall for quality of life in several studies [3–7]. In a population-based survey using the Parkinson's Disease Quality of Life Questionniare (PDQ-39) and the Beck Depression Inventory (BDI), Schrag and colleagues [5] found that the factor most strongly related to poorer quality of life was depression, although motor disability was also significantly associated. In a model predicting PDQ-39 scores, the BDI score accounted for 54% of the variance, whereas motor disability scores accounted for only 15%. The Global Parkinson's Disease Survey Steering Committee [6] also found the BDI score to be the most significant predictor of quality of life, accounting for 58% of the variance in PDQ-39 scores, whereas stage of motor severity and PD medication (levodopa, either alone or in combination with other dopaminergic drugs) together explained only 17% of the variability of quality of life in PD.

Besides depression, anxiety disorders are a clinically significant problem in patients with PD. The prevalence of anxiety has typically been found to be 20–46% of PD patients [8–12] though other studies have reported rates of up to 75% [13]. The number of patients with PD who experience significant anxiety is greater than that of individuals with other chronic medical conditions such as multiple sclerosis or of the general population [13]. Anxiety is thought to have an important impact on motivation, treatment compliance, and cognition and can exacerbate parkinsonian symptoms [14].

The contribution of anxiety to quality of life in PD has been less studied, although anxiety symptoms have been found to have a significant association with poorer quality of life in the general population [15]. Most of the few studies that include measures of both anxiety and quality of life have

assessed changes in anxiety and quality of life as markers of treatment outcome following a surgical intervention to diminish motor symptoms, rather than directly examining the relation of anxiety to quality of life. One such study by Higginson and colleagues [16] found that improvement in symptoms of anxiety following surgical treatment of PD reflected a true reduction in anxiety as opposed to being simply a reaction to PD motor-symptom amelioration. More recent studies suggest that anxiety contributes to impaired quality of life in PD, using general psychiatric surveys rather than specific anxiety-related instruments [17, 18]. Anxiety symptoms are often comorbid with depression symptoms and the cooccurrence of these disorders is typically characterized by a more chronic course with significant impairment in social and occupational functioning [19]. Improved understanding of the aspects of such symptoms that impact quality of life would lead to increased attention and diagnosis of mood disorders in PD and to formulation of more appropriate treatment plans.

The aim of the present study was to investigate the relation of anxiety and depression to health-related quality of life in PD. Clinical variables that may impact quality of life were explored, including overall cognitive status, disease severity, and side of motor onset, as well as age, education level, and gender. Some studies [16, 20] suggest that certain commonly used measures of anxiety (Beck Anxiety Inventory [BAI]) and depression (Beck Depression Inventory [BDI]) may inflate the prevalence of anxiety and depression symptoms in PD because of the overlap of somatic symptoms of anxiety and depression with disease-related motor symptoms of PD such as trembling or wobbliness in the legs. For this reason, the present study included the Spielberger Anxiety Inventory-Trait (STAI) and the Geriatric Depression Scale (GDS), which are two self-report measures that include fewer somatic items [21–23], in addition to the BAI and BDI. The intention was to establish PD compromise on mood measures without somatic load before concluding that mood itself was directly related to quality of life [16, 20, 24]. We hypothesized that anxiety symptoms, like depression, would predict quality of life more strongly than would motor symptoms. We further expected to find anxiety to uniquely contribute to quality of life in PD.

2. Methods

2.1. Participants. Thirty-eight nondemented individuals (20 men, 18 women) participated in the study. All participants were recruited from the Boston Medical Center Neurology Clinic and from local PD support groups. Each participant's medical record was reviewed to confirm the diagnosis of idiopathic PD. Informed consent was obtained from each participant. No individual had undergone surgery affecting the thalamus, basal ganglia, or other brain regions. Motor disability was staged using the Hoehn and Yahr scale [25]. At the time of testing, the motor response was at its optimum ("on" period).

The widely used Mini-Mental State Examination (MMSE [26]) was administered as a brief screen for dementia, which allows us to compare directly the mental status of our sample to those reported in the literature. An MMSE score of 25 or better, indicating nondemented status, was required to participate. Participants were questioned about psychiatric history and current psychotropic medication.

2.2. Measures. The Dementia Rating Scale (DRS [27]) assesses cognitive functioning in five domains: attention, initiation/perseveration, construction, conceptualization, and memory. The DRS was chosen as the cognitive status variable because it is a widely used and accepted measure for the assessment of neurocognitive functioning in the geriatric population and it has demonstrated good validity in PD patients [28].

The Hoehn and Yahr scale (H/Y) is a standard clinical index of PD motor stage. It globally indexes signs and symptoms of functional impairment, including postural instability, rigidity, tremor, and bradykinesia. Stage I indicates unilateral motor involvement. Stages II and III indicate mild and moderate bilateral disability, respectively. None of our participants was categorized as higher than Stage III (see Section 3).

The 21-item Beck Anxiety Inventory (BAI [29]) assesses anxiety in normal populations. A higher overall score indicates more symptoms of anxiety. The BAI consists of items that represent physiological symptoms such as numbness and tingling, dizziness, and sweating, and items representing "subjective" symptoms of anxiety such as fear of the worst happening, fear of losing control, or feeling scared [29] The Spielberger Anxiety Inventory-Trait (STAI-T [30]) is a 20-item self-report instrument designed to assess trait anxiety. The items are summed to produce a total score, with higher scores indicating more trait anxiety. The STAI-T was included as a measure of anxiety because it does not include somatic items. The STAI-T was developed from the premise that anxiety is the affective response when there is a perceived or actual discrepancy between external demands and coping resources and focused less on the physiological symptoms of anxiety.

The Beck Depression Inventory II (BDI-II [31]) was administered to assess depression symptomatology. The test contains 21 items, most of which assess depressive symptoms on a Likert scale of 0–3. The BDI-II includes 13 items that pertain to somatic symptoms of depression. The Geriatric Depression Scale (GDS [32]) is a 20-item measure of depression that was developed for the geriatric population and omits questions regarding sleep and appetite disturbance, which are symptoms that may result from PD motor symptoms or side effects of PD medication rather than reflecting the presence of depression in PD. Only two items may capture somatic symptoms (energy; restless and fidgety). Conservative cut-off scores were used with the Beck measures when determining the percentage of the sample to have clinically significant levels of anxiety and depressive symptoms [16, 20].

The Parkinson's Disease Quality of Life Questionnaire (PDQ-39 [33]) is a disease-specific, 39-item questionnaire on the quality of life in PD. Quality of life is a multidimensional concept that reflects a patient's subjective evaluation of well-being, satisfaction, functioning, and impairment [34].

Dimensions assessed include mobility, activities of daily living, emotional well-being, stigma, social support, cognitive impairment (arousal, concentration, memory, and dreaming/hallucinations), communication, and bodily discomfort. Lower scores on the PDQ-39 indicate greater quality of life. Summing all eight of the PDQ-39 dimensions and standardizing the score on a scale of 0–100 creates the summary index score of the measure (PDQ-39SI). The PDQ-39SI provides insight into the overall impact of the illness as measured by each of the domains included. The PDQ-39 is the most widely used disease-specific health status questionnaire in the literature and has demonstrated high reliability and validity in PD [33].

2.3. Scoring and Statistical Analysis. The summary index of the PDQ-39 was calculated according to the standard scoring algorithm [35]. All variables were converted to standardized z scores. Spearman rank correlation coefficients were calculated to assess the direction and magnitude of association between variables. A stepwise hierarchical regression analysis was performed, with variables entered into the regression model in the order of interest (anxiety first, then depression) in accordance with information provided by our preliminary findings [36]. Mann-Whitney U test analyses were conducted to determine if side of motor symptom onset, disease duration, age at onset, current age, or gender were associated with the extent of anxiety or depression symptoms.

3. Results

3.1. Descriptive Analysis. Thirty-eight participants with idiopathic PD were evaluated (Table 1). Participants included two in Stage I (unilateral), 27 in Stage II (mild bilateral), and nine in Stage III (moderate bilateral). For 22 of the participants, motor symptom onset was on the left body side, for 15 onset was on the right side, and for one onset was reported to be bilateral.

Twelve participants followed a medication regimen that included a combination of levodopa/carbidopa therapy alone ($n = 2$) or in combination with one other dopamine agonist (pramipexole ($n = 3$), pergolide ($n = 1$), or ropinirole, ($n = 2$)). Five participants were treated with levodopa/carbidopa therapy and the catechol-O-methyltransferase inhibitor entacapone, two participants were treated with this regimen (levodopa/carbidopa plus entacapone) and dopamine agonists, and one with this regimen and the anticholinergic trihexyphenidyl. Six participants were treated with trihexyphenidyl plus either levodopa/carbidopa ($n = 1$) or the dopamine agonist pramipexole ($n = 1$). Nine participants received levodopa/carbidopa therapy in combination with additional dopaminergic medications and either the monoamine oxidase type B inhibitor selegiline ($n = 3$) or amantadine ($n = 1$), which stimulates dopamine release. Six individuals were being treated with a dopamine agonist alone and either selegiline ($n = 1$), trihexyphenidyl ($n = 1$), or amantadine ($n = 1$).

The mean PDQ-39 score was 262.8 (standard deviation 126.3), mean MMSE was 29.0 (1.3), and mean DRS was 141.7 (2.6). The mean depression scores on the BDI-II and GDS were 10.6 (7.0) and 9.3 (6.7), respectively. The mean anxiety score was 14.2 (8.1) on the BAI and 37.0 (10.6) on the STAI-T. Because of the issue of somatic items, we followed the recommendation for higher cut-off scores for each Beck measure in PD [16, 20], which provides greater specificity albeit with decreased sensitivity. Eleven participants (29% of the sample) had clinically significant anxiety when evaluated with the BAI using a highly specific cut-off score of 18 [16] compared to 12 (32%) determined by the STAI-T cut-off score 42. Clinically significant depression was present in eight (21%) when determined by the BDI-II with a highly specific cut-off score of 17 [16] and in 17 (45%) when measured by the GDS with a standard cut-off score of 10, which has yielded 100% sensitivity and 84% specificity for a diagnosis of major depression in primary care settings [37].

Table 1: PD participant characteristics; means (SD).

N	38
Age, years	62.1 (8.7)
Education, years	16.3 (2.9)
MMSE (total)	29.0 (1.3)
Men:women	20 : 18
Disease duration, years	8.4 (6.4)

MMSE: Mini-Mental State Examination.

Patients on antidepressants were all stable on their medication for at least six months and did not differ on their mood scores from those not on antidepressants. A total of ten participants were taking antidepressant medication, which included either paroxetine or sertraline. Despite the medication, two participants still had clinically significant anxiety, three had clinically significant depression and anxiety, and two had clinically significant depression, leaving three without significant levels of anxiety and depression with the psychiatric medication.

Comorbidity of anxiety and depression can be a concern; we used the Beck measures because they have demonstrated good divergent validity in regard to detection of anxiety and depression. Six participants (16% of the sample) had clinically significant anxiety without clinically significant depression, three participants (8%) had clinically significant depression without clinically significant anxiety, five (13%) had both clinically significant anxiety and depression, and 24 (63%) did not have clinically significant anxiety or depression. Hence, there were more participants with principally more anxiety than depression in this sample.

The percentage of anxiety and depression in the present sample did not differ for men and women, nor for those with motor symptom onset on the right versus the left side of the body (Table 2), nor did there appear to be any interaction of gender and side of onset. No significant differences were found between the gender or side of onset subgroups on quality of life. Mann-Whitney U test analyses revealed that side of motor symptom onset, age at onset, and gender were not associated with the extent of anxiety or depression symptoms. Data were accordingly collapsed across these variables for subsequent analyses.

Table 2: Anxiety and depression symptoms in PD subgroups by gender and side of motor symptom onset.

	Male ($n = 20$)	Female ($n = 18$)	LPD ($n = 21$)	RPD ($n = 16$)
BDI-II	11.8 (7.3)	9.2 (6.5)	10.3 (7.4)	11.0 (6.8)
GDS	10.0 (6.2)	8.6 (7.3)	9.8 (7.6)	9.0 (5.7)
BAI	15.0 (7.4)	13.2 (9.0)	15.1 (9.2)	13.1 (6.9)
STAI-T	38.1 (7.9)	35.8 (13.1)	37.6 (11.4)	36.8 (9.9)

BDI-II: Beck Depression Inventory; GDS: Geriatric Depression Scale; BAI: Beck Anxiety Inventory; STAI-T: Spielberger Trait Anxiety Inventory; LPD: left motor symptom onset PD; RPD: right motor symptom onset PD.

3.2. Correlation Analysis Results. Motor symptom stage, age, education, duration of disease, anxiety, depression, and overall cognitive status are variables that have previously been shown to affect health-related quality of life and were included in the correlational analysis (Table 3). The PDQ-39 summary index score correlated significantly and positively with anxiety as measured by the BAI ($\rho = .54$, $P < .0001$) and the STAI-T ($\rho = .65$, $P = .002$) and with depression as measured by the BDI-II ($\rho = .54$, $P < .0001$) and the GDS ($\rho = .43$, $P < .0001$). The PDQ-39 was inversely related to overall cognitive status (DRS) ($\rho = -.33$, $P = .005$), though it should be noted that none of the participants met the criteria for dementia, including scores on the DRS or MMSE. Those suffering from more symptoms of anxiety and depression demonstrated poorer quality of life. Age of disease onset ($\rho = -.16$, $P = .35$), current age ($\rho = -.04$, $P = .81$), duration of disease ($\rho = .17$, $P = .32$), education ($\rho = -.11$, $P = .51$), and motor stage (H/Y score; $\rho = -.10$, $P = .55$) did not correlate significantly with quality of life. Years of education was inversely correlated with symptoms of anxiety as measured by the BAI ($\rho = -.43$, $P = .007$) but not the STAI-T ($\rho = -.27$, $P = .11$) or symptoms of depression (GDS, $\rho = -.22$, $P = .19$; BDI-II, $\rho = -.17$, $P = .31$).

3.3. Multiple Regression Analysis Results. Using multiple regression, the quality of life summary score was then regressed on the linear combination of variables suggested by the literature to impact quality of life including anxiety symptoms (BAI), depression symptoms (BDI-II), motor stage (H/Y), and cognition (DRS). The equation accounting for these four variables accounted for 49% of the variance in quality of life ($F(4, 38) = 9.92$, $P < .001$, adjusted $R^2 = 0.49$). Because of the good divergent validity of the Beck measures for detecting symptoms of anxiety and depression and our desire to be as conservative as possible in designation of clinical anxiety and depression, we used the Beck measures rather than the STAI-T or GDS for the regression analyses. This decision was supported by our finding that the STAI-T correlated significantly with the GDS ($r = .79$, $P = .000$).

Only variables that correlated significantly with the PDQ-39 quality of life measure were entered into the stepwise multiple regression analysis. These variables included the anxiety score (BAI), the depression score (BDI-II), and the overall measure of cognitive status (DRS). Anxiety and depression demonstrated nearly equivalent beta-weights with the BDI-II at 0.37 ($t = 2.39$, $P < .05$) and BAI at 0.34 ($t = 2.23$, $P < .05$). The beta-weight for overall cognition (DRS) was -0.24 ($t = 1.78$, $P > .05$), which indicated that cognition did not significantly contribute to the model. All coefficients were in the predicted direction. Overall, anxiety symptoms accounted for 29% of the variance in quality of life beyond the variance accounted for by the other predictors. Following the variance accounted for by anxiety, depression symptoms uniquely accounted for an additional 10% of the variance in quality of life.

4. Discussion

We found that symptoms of anxiety, more than depression, overall cognitive status, or motor stage, affect health-related quality of life for nondemented patients with PD. The hypothesis that anxiety symptoms would significantly explain variance in overall quality of life (PDQ-39) in PD was supported, in that anxiety explained 29% of the variance beyond that explained by the other clinical variables in the model. Depression explained an additional 10% of the variance not accounted for by anxiety. Together, these mood symptoms accounted for 39% of the variance in quality of life. Although cognitive status (DRS scores) correlated significantly with quality of life scores, it did not explain any further variance when anxiety and depression were in the model, and in any case none of the participants met criteria for dementia.

Earlier studies describing quality of life in patients with PD did not include both anxiety and depression in the model. Without including anxiety scores, the majority of these studies found either depression [2–5, 7] or disease severity [3–5] to be the most frequent associate of quality of life. Some previous studies have shown cognitive status, as measured by MMSE, to be an important predictor of quality of life in PD [5], but others have not [4].

Studies have found depression to explain up to 50% of the variance in PDQ-39 scores [1, 3, 5, 38]. The current study found depression symptoms to predict only 10% of the variance once anxiety was accounted for. Although differences in sample sizes from study to study may underlie some differences in the size of the contribution of depression, it may also be argued that, if previous studies had included an anxiety score in their model, their results may have been more similar to those of the present study. It is also possible that, because depression and anxiety symptoms often occur together in PD (e.g., [10]), the measures used to capture anxiety and depression are not able to differentiate these two conditions, or an interaction between the two is present. Arguing against this interpretation is the fact that the Beck

Table 3: Spearman correlation matrix for variables previously demonstrated to affect health-related quality of life in PD.

	STAI-T	BDI-II	GDS	DRS	H/Y	AGE	EDU	DUR	PDQ-39
BAI	.68**	.54**	.43**	−.33*	−.31	0.05	−.43**	.19	.54**
STAI-T		.78**	.79**	.23	.13	.05	−.27	−.01	.65**
BDI-II			.79**	−.20	.09	.17	−.17	−.02	.54**
GDS				−.02	−.08	.09	−.22	.08	.43**
DRS					−.37*	−.28	.17	−.24	.33*
H/Y						.16	−.005	.21	−.10
AGE							−.09	.33*	−.04
EDU								−.09	−.11
DUR									.17

* $P < .05$; ** $P < .01$.

BAI: Beck Anxiety Inventory; STAI-T: Spielberger Trait Inventory; BDI-II: Beck Depression Inventory II; GDS: Geriatric Depression Scale; general cognitive status: DRS: Dementia Rating Scale; H/Y: Hoehn and Yahr index of motor symptom stage; AGE: age at time of testing; EDU: years of education; DUR: years of disease duration.

measures used in the present study have demonstrated good divergent validity between anxiety and depression [39].

In spite of the relatively high mean DRS scores for the sample, cognitive status was significantly associated with quality of life, consistent with Schrag and colleagues [5] even though it did not significantly contribute to the model once the mood measures were included. A sample comprising a larger range of cognitive impairment related to PD, including dementia, may show a greater impact of cognitive status on reported quality of life. It should also be noted that brief screening measures such as those used here do not capture more subtle cognitive changes that could contribute to patients' reported well-being. Future studies with tests that assess specific cognitive domains may not only further elucidate the relation of cognition to quality of life but also help determine whether various types of cognitive difficulties—for example, executive functioning versus attention—differentially impact reported quality of life in PD.

We did not find a relation between overall quality of life and motor stage, as measured by the Hoehn and Yahr (H/Y) scale. A study by Hobson and Meara [40] did not find any significant correlation between motor stage, using the H/Y scale, and scores of the SF-36, the Short Form health related quality of life scale, whereas a study by the Global Parkinson's Disease Research Committee [6] found H/Y scores and medication to explain up to 17.3% of the variance in the PDQ-39. In our recent study, we found correlations between only some aspects of motor severity as indexed by the UPDRS and some of the PDQ-39 subscales: specifically, the Rigidity and Dopamine-dependent subscales of the UPDRS with the ADL subscale of the PDQ-39; the Rigidity and Facial Expression subscales of the UPDRS and the Communication subscale of the PDQ-39 [41]. A sample with a wider range of motor severity than represented in our present sample may well yield different results.

Anxiety is prevalent in PD, and this study highlights the dramatic impact it has on quality of life. Despite using conservative cut-off scores and using measures with few somatic items, clinically significant anxiety occurred in one-quarter to one-third of the participants of this study, depending on the measure used. Exactly how anxiety impacts quality of life has yet to be clearly determined. Anxiety symptoms are more prevalent in PD patients than in the general population or in individuals with other chronic illnesses but are not primarily a psychological reaction to the illness or side effects of levodopa treatment [42]. Some investigators suggest that people with anxiety and people with PD share an underlying biological vulnerability. Anxiety and affective symptoms have been associated with striatal dopamine transporter (DAT) availability in the basal ganglia [43] as well as with PD-related loss of catecholinergic cells of the locus ceruleus [12, 13] and abnormalities of serotonin production [13]. It is of substantial interest that mood disorders may precede the onset of PD motor symptoms by several years—even 20 years in the case of anxiety—suggesting that mood disorders may be prodromal indicators of PD [44, 45]. Besides anxiety itself, an anxious (neurotic) personality has also been revealed as a risk factor for PD much later in life [46], again suggesting a common pathophysiology for anxiety disorders and PD.

A more direct relation between anxiety symptom amelioration and improvement in PD symptoms may exist than previously recognized. Anecdotal evidence coupled with a study by Knight et al. [42] suggests that motor symptoms themselves may be influenced by anxiety in PD. For example, the disabling motor symptoms such as tremor, rigidity, bradykinesia, and postural instability, which often occur intermittently, have been shown to increase when the patient is concentrating or feeling anxious [10]. Further research exploring the direct relation of anxiety and motor symptoms and subsequent quality of life needs to be conducted. It is possible that treatment of anxiety in PD not only will increase the perceived quality of life but also may help reduce the frequency of the motor symptoms associated with the disease.

With 39% of the variance in quality of life accounted for by anxiety and depression symptoms, this study highlights the importance of treating anxiety symptoms as a means to improving the well-being of patients with PD as well as the importance of continued emphasis on the impact

of depressive symptoms on their overall well-being. Some investigators have suggested a more pronounced increase in comorbidity of anxiety and depression in patients with PD than in healthy adults (19.3% comorbidity in PD versus 8.6% in control adults) [47]. When depression and anxiety occur together, they are associated with increased impairment, a more chronic course, and poorer outcome, rendering treatment more complex [48–50]. In PD, investigators have suggested that anxiety often presents before the onset of comorbid depression [51]. The strong comorbidity between generalized anxiety disorder and major depression, the fact that most people with this type of comorbidity report that the onset of generalized anxiety disorder occurred before the onset of depression, and the fact that primary generalized anxiety disorder significantly predicts the subsequent onset of depression and other secondary disorders raise the question of whether early intervention and treatment of primary anxiety would effectively prevent the subsequent onset of secondary depression as well as improve PD patients' quality of life.

Limitations of this study include the use of patient self-report and the sample size. Future research can address this issue by including more participants and adding measures of participants' dispositional characteristics. The use of a brief self-report measure of anxiety and depression, although practical, does not allow us to clarify the nature of the anxiety and depressive disorder in this population or to determine whether the specific type of anxiety disorder has a differential impact on quality of life—for example, generalized anxiety disorder versus social phobia versus panic disorder, though all have been associated with PD [11, 52–54]. Replicating this study with a clinician-based interview would help elucidate whether certain types of anxiety disorders have greater impact on quality of life and more confidently clarify the frequency of general anxiety disorder and major depressive disorder in PD. It would also be worthwhile to include a more sensitive measure of PD motor symptoms, such as the UPDRS. In a larger sample, it would be of interest to examine data on disease characteristics associated with anxiety, such as motor fluctuations and dyskinesias. Although the results of this study indicate that mood symptoms are associated with reduced quality of life in patients with PD, this study is cross-sectional and the direction of causation among the variable examined cannot be determined. Longitudinal studies would help clarify the causal relation between the variables in this study and help us to assess how quality of life may change following treatment of anxiety and depression in this population.

A better understanding of the factors that have the greatest impact on a patient's well-being is important to informing new and improved treatment management plans in PD. The findings of the present study support those of other studies in the literature that mood symptoms are better predictors of quality of life than is motor symptom stage [1–3, 5]. The primary difference between this study and previous studies is the inclusion of standard anxiety measures here and the finding that anxiety, in addition to depression, is associated with quality of life using a PD-specific quality of life measure.

Despite the prevalence of anxiety and depression in PD, mood symptoms are often not addressed in individuals with this disease. In a chronic and disabling illness such as PD, improving the aspects of well-being that most significantly impact their perceived quality of life is vital [12]. Empirical studies confirm that cognitive behavioral therapy (CBT) is an effective form of therapy for the treatment of anxiety and depression in the general population [55, 56]. Dobkin et al. (1997) demonstrated the effectiveness of CBT for the treatment of depression in PD [57], but further studies are needed to also address the effectiveness of CBT and other therapies for the treatment of anxiety in PD. The findings of the present study suggest that primary assessment and management of the anxiety and depression associated with the disease may be needed to optimize the quality of life of patients with PD, and we accordingly call for more clinical work and research in this area. As there is no cure for PD, empirically supported treatment of distressing neuropsychiatric symptoms is of paramount importance in the quest to improve the quality of life of individuals with this disorder.

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Review Article

Cognitive Rehabilitation for Executive Dysfunction in Parkinson's Disease: Application and Current Directions

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Cognitive dysfunction in Parkinson's disease contributes to disability, caregiver strain, and diminished quality of life. Cognitive rehabilitation, a behavioral approach to improve cognitive skills, has potential as a treatment option to improve and maintain cognitive skills and increase quality of life for those with Parkinson's disease-related cognitive dysfunction. Four cognitive rehabilitation programs in individuals with PD are identified from the literature. Characteristics of the programs and outcomes are reviewed and critiqued. Current studies on cognitive rehabilitation in PD demonstrate feasibility and acceptability of a cognitive rehabilitation program for patients with PD, but are limited by their small sample size and data regarding generalization of effects over the long term. Because PD involves progressive heterogeneous physical, neurological, and affective difficulties, future cognitive rehabilitation programs should aim for flexibility and individualization, according to each patient's strengths and deficits.

1. Introduction

Cognitive dysfunction is a nonmotor feature of Parkinson's disease (PD) that contributes significantly to disability, caregiver strain, and diminished quality of life over the course of the disease [1, 2]. While there is not a "signature" deficit that characterizes cognitive dysfunction in PD, common features include executive dysfunction, visuospatial dysfunction, and short-term memory deficits. Even in the earliest stages of PD, cognitive decline, and executive dysfunction in particular, is present in up to a third of patients [3]. An estimated 50% of individuals with PD have mild cognitive impairments in the absence of dementia [4, 5], and 25–30% of individuals with PD meet criteria for dementia [6, 7].

With advances in medical and surgical interventions for motor symptoms, individuals with PD are living longer and facing greater disability related to cognitive impairments. Accordingly, there is a corresponding need to address cognitive changes therapeutically. Yet, to date, there are no definitive treatments for cognitive dysfunction in PD [8]. Medication trials, aimed at slowing progression of cognitive decline or improving cognitive performance, have had variable success in decreasing functional impairment [8, 9]. Alternative or adjunctive behavioral interventions for cognitive dysfunction have the potential to reduce disability and improve quality of life in individuals with PD and their caregivers. Originally developed to improve cognitive functioning after traumatic brain injury (TBI), cognitive rehabilitation programs have recently been adapted for other neurological conditions [10]. However, there are no standardized guidelines regarding the types of strategies that offer the most beneficial outcomes, or the types of cognitive

impairments or stages of cognitive decline for which treatment is most beneficial that would guide application in PD.

Cognitive rehabilitation, a behavioral treatment approach for individuals with cognitive dysfunction, is designed to reduce functional impairment and increase engagement in daily adaptive activities. Although there is variation across programs, the essential elements of cognitive rehabilitation consist of basic skills training related to performance of vocational, social, and adaptive daily living skills. Subsets of cognitive training programs target improvements in specific cognitive domains, including visuospatial awareness, attention, working memory, or executive functioning, which are the essential cognitive skills to complete daily living tasks. Cognitive rehabilitation strategies consist of restorative or compensatory techniques. Restorative techniques focus on strategies to improve cognitive functioning to closer to the patient's level before there was an obvious decline. Specific restorative skills include techniques to improve recall of information over increasing periods of time (spaced retrieval) or using less intense cues (vanishing cues), computerized drills and repeated prompting to improve memory and attention and recall of remote memories (reminiscence therapy). Compensatory techniques provide strategies that organize information to improve recall and learning and provide instruction in self-management strategies. Compensatory techniques also include using multiple senses to improve learning and retrieval, procedural training to learn increasingly more complex behaviors, and external cues such as memory notebooks or calendars to improve recall. Programs may also teach, in-person or with the aid of computerized devices and software, strategies to improve self-management, such as problem solving, time management, and compensation for impaired memory [11]. Examining which cognitive strategies have the most beneficial impact on cognitive functioning, and adaptive living skills for PD could be the initial step in evaluating the feasibility and utility of cognitive rehabilitation programs in this population.

The short- and long-term cognitive impairments following traumatic brain injury (TBI) are optimal targets for cognitive remediation, and positive outcomes following cognitive rehabilitation have been consistently demonstrated [10]. Standard TBI rehabilitation programs include training in strategies to compensate for attention deficits, visual scanning (for visual neglect), apraxia, language and functional communication, and mild memory deficits [12]. As TBI patients often have executive dysfunction, inclusion of emotional self-regulation and motivation skills into problem-solving skills has been shown to be effective in TBI cognitive training programs [10, 13]. While numerous cognitive rehabilitation programs have been developed for TBI, which is an acquired brain injury; less research has focused on progressive neurological disease.

Cognitive rehabilitation programs for neurological disorders, including studies in Alzheimer's disease (AD), vary considerably in content (memory, learning, executive functioning, attention), administration (individual, group, computerized), timing (1 session versus 15 sessions) and setting (inpatient versus outpatient) [14, 15]. In Alzheimer's disease (AD), the studies have used primarily restorative strategies with both individual and group cognitive training programs have demonstrated positive outcomes [14, 15]. These cognitive training programs in AD provide evidence that patients with progressive neurological conditions can benefit from retraining. However, memory-training strategies are the primary cognitive skill evaluated in AD and rehabilitation studies have not evaluated executive functioning in this population.

Lack of agreement regarding the definitions of PD-cognitive dysfunction and procedures (e.g., structured interviews, expert consensus, or neuropsychological tests) that best identify cognitive changes and impairments is a major challenge to treatment. This is particularly evident in PD-Mild Cognitive Impairment (PD-MCI), which has been defined inconsistently across studies. In general, MCI refers to an intermediate severity of acquired cognitive dysfunction between the cognitive status of "within normal limits" and "demented." Whereas the MCI classification was developed and validated for conversion to Alzheimer's disease (AD) [16], similar nomenclature and criteria were proposed for PD-MCI [17].

Prevalence of PD-MCI and more subtle cognitive dysfunction in PD ranges from 21% to 55%, depending on the duration of the disease and which PD-MCI criteria and neuropsychological measures were used [4, 17, 18]. PD-MCI criteria have been outlined as the presence of a subjective report of cognitive problems by the patient or caregiver and performance at least 1.5 standard deviations below the age-corrected mean score in one cognitive domain without impairments in activities of daily living [17]. On the basis of these criteria, 21% of PD patients met criteria for PD-MCI and 17% met criteria for PDD [17].

In patients with PD-MCI, executive dysfunction/attention and memory impairment are the most prevalent deficits reported [4, 17]. By contrast, when PD-MCI is defined as performance that is only one standard deviation below the age-corrected mean across several neuropsychological measures [19], 53% of PD patients were classified as PD-MCI and the amnesic subtype was most prevalent, followed by the executive function and visuospatial subtypes. However, neither of these PD-MCI criteria identifies individuals whose test performance is significantly declined from a higher premorbid baseline but has yet to fall one or more standard deviations below normative test performance.

Cognitive deficits are noticed in daily life when they result in impaired performance in job-related duties, activities of daily living, and other activities that contribute to an individual's level of independence and well-being. For example, safety, financial planning and paying bills, driving, and occupational performance can be of concern in patients who demonstrate impairments in executive functions [20–23]. Accordingly, an approach to classification of cognitive dysfunction that overcomes the limitations of normative assessments focuses on functional change. With this approach, a functional change in performance that does not meet the PD-MCI criteria is described as subtle cognitive dysfunction [24]. Thus, individuals who have normal psychometric performance but who use compensation strategies or increased effort to avoid the functional impact of cognitive

deficits would be captured with this classification. It would be helpful to identify what types of impairments from subtle to PD-dementia are most likely to benefit from cognitive rehabilitation.

This integrative paper provides an overview of the types of cognitive impairments that are targeted in rehabilitation for cognitive dysfunction in PD and compares the content and delivery methods of cognitive rehabilitation interventions applied to patients with PD. Strengths and limitations of the current literature and future directions for cognitive rehabilitation in PD are discussed.

2. Methods

To identify relevant studies for the integrative review, keyword searches of abstract and titles were conducted in the PubMed and PsycINFO databases for studies published prior to July 2011. We used search terms (1) "Parkinson's disease" and "cognitive training", (2) "Parkinson's disease" and "cognitive rehabilitation", (3) "Parkinson's disease" and "cognitive remediation," (4) "Parkinson's disease" and "training" and "executive." Articles were included if they were original research in English, included individuals with Parkinson's disease, and described any type of intervention for cognitive functioning with pre- and postassessments.

3. Results

The PubMed search yielded a total of 18 unique articles and 3 additional studies were found in the PsycINFO database. Of the 21 abstracts reviewed, 17 were excluded. Reasons for exclusion were not reporting original research (e.g., review manuscripts, $n = 5$), not being in English ($n = 2$), not reporting cognitive rehabilitation interventions (e.g., interventions for gait, $n = 6$), not including pre- and postsassessments ($n = 2$), and subject population not individuals with Parkinson's disease ($n = 2$).

3.1. Cognitive Rehabilitation in Parkinson's Disease. To date, there have been four reports of cognitive rehabilitation or training programs for patients with PD. Two are open-trial pilot studies, and two are small randomized controlled trials (RCTs) of cognitive rehabilitation programs targeting executive functioning, attention, and visuospatial abilities (see Table 1).

In Sinforiani and colleagues' open trial [25], 20 patients with idiopathic PD who were enrolled in a day hospital motor rehabilitation program completed a computerized cognitive rehabilitation program that focused on improving attention, abstract reasoning, and visuospatial abilities. After cognitive training, PD patients had significantly improved verbal fluency, immediate and delayed logical memory, and visuospatial reasoning compared with their baseline assessments; these gains were maintained after 6 months. Although no differences were found after cognitive rehabilitation on measures of short-term memory, set-shifting or inhibition, this study suggests the potential for patients with PD to complete cognitive rehabilitation, improve performance on cognitive assessments, and maintain those gains. However, the small sample size, lack of a control comparison group, inpatient setting, and absence of a measurement of everyday functioning limit conclusions with respect to overall cognitive and functional improvement enhanced by the cognitive rehabilitation program and generalization of these findings to the larger population of PD patients who are not in an inpatient setting.

Mohlman et al. [26] completed a small ($n = 14$) open trial to test the feasibility of an attention process training intervention for patients with a minimental state exam (MMSE) score >23 and idiopathic PD. The intervention consisted of in-person training with practice exercises and worksheets on attention tasks. Daily at-home practice exercises were also encouraged for all participants. Fourteen participants completed the program, and the self-report ratings on feasibility yielded positive results. The average rankings were between "some" to "much" perception of progress in improving their attention and enjoyment. The author reported that the participants improved on the measures of executive skills consisting of Digit Span backward, Stroop Color Word Test, Trail Making B, and Controlled Oral Word Association Test. This open trial successfully demonstrated the feasibility of administering an in-person cognitive training program and patients' acceptance of training. However, because of the small sample, study design and minimal outcomes measures, in addition to the lack of control group and long-term followup, conclusions as to the effectiveness of the intervention and translation into short-term or long-term functional outcomes are limited.

The two RCTs investigating cognitive rehabilitation in PD included relatively small sample sizes; however, these studies improved upon the literature by comparing the benefits of cognitive training programs to usual care received by individuals with PD. Sammer and colleagues [27] conducted an RCT for cognitive training of executive functions in the context of an inpatient rehabilitation program for PD. Participants were randomized to receive standard rehabilitation (occupational therapy, physiotherapy, and physical treatment) or standard rehabilitation plus a cognitive training program. The cognitive training program consisted of 10 sessions focused on facilitating working memory functioning, including search tasks, matrices, puzzles, speech production, picture completion, and storytelling. The 12 patients who completed the program demonstrated improved executive function compared with the 14 patients who completed only the standard treatment, even after controlling for premorbid intelligence, mood, age, dopaminergic medications, and disease severity. Additionally, the standard treatment arm had reduced working memory performance; whereas patients who received cognitive training maintained their baseline scores aftertreatment. This pilot RCT study was limited by a small sample size and lack of long-term assessments to evaluate maintenance of gains. Furthermore, the study did not address whether the treatment contributed to generalized improvements in daily activities or outside the inpatient setting.

Another small RCT compared a 4-week outpatient computer-based cognitive training program to a speech

Table 1: Cognitive training programs for patients with Parkinson's disease.

Author(s)	Total *N*	Randomized study	Length of treatment	Treatment	Cognitive targets	Outcome measures	Results
McKinlay et al. [24]	20	No	12 1-hour sessions over 6 weeks	Computerized software for neuropsychological training	Attention, abstract reasoning, visuospatial	Babcock's story, FAS, Raven matricies, Corsi-test, WCST and Stroop	PD patients improved on Babcock's story, FAS* and Raven matrices and at 6 months gains maintained. No differences from baseline on digit span, Corsi-test, WCST* and Stroop after training
Sinforiani et al. [25]	14	No	4 90-minute sessions over 4 weeks	Attention process training	Sustained, selective, alternating, and divided attention	Digits backward, Stroop, Trail Making Test B, FAS	Improvement on digits backward, Stroop, Trail Making Test B and FAS post treatment. On average, self-ratings were given for "some" to "much" progress, enjoyment and effort in the program
Mohlman et al. [26]	26	Yes 12 cognitive training 14 standard treatment	10 30-minute sessions during a 3-4 week rehabilitation hospital stay.	Working memory tasks	Executive functions	BADS	Cognitive training group significant improvement on BADS*
Sammer et al. [27]	33	Yes 18 cognitive training group15 control group	12 45-minute sessions over 4 weeks	Computerized software and paper-pencil exercises	Attention/ working memory, memory, psychomotor speed, executive functions and visuospatial	Digits Forward, Stroop, ROCFT, Semantic fluency, Trail Making B, TOL, PDQ-39 and CDS	Cognitive Training group had more improvement than Control Group after treatment on the Digit Span Forward, Stroop Word Test, ROCFT, Semantic fluency, Trail Making B and TOL. No group differences on the PDQ-39 or CDS

** Note*: BADS: behavioral assessment of dysexecutive syndrome, FAS: phonological word fluency test; WCST: wisconsin card sorting task; ROCFT: Rey-Osterrieth complex figure test, TOL: tower of London, PDQ-39: Parkinson's disease questionnaire-39; CDS: cognitive difficulties in ADLs.

therapy program matched on participation time [28]. All 33 participants had idiopathic PD and MMSE greater than 23. Among the subjects, 50% met criteria for MCI; but MCI was not a significant predictor in the outcome analysis. Following the 4-week intervention, the 18 participants in the cognitive training group demonstrated improved performance on attention, information processing, visual memory, verbal fluency, visuoconstruction, and executive functioning measures. Participants with and without MCI improved equally well-following treatment. The study had no long-term outcome assessments.

4. Conclusions

Cognitive rehabilitation programs are increasingly recognized as beneficial alternatives to or adjunctive therapy for medications for improving specific types of cognitive dysfunction in patients with neurological disorders or maintaining patients at their current level; however, there is limited evidence for the effectiveness of cognitive rehabilitation in PD. The cognitive training programs for TBI and AD, which utilize the most well-developed programs have shown improvements in memory, attention, executive functioning, and problem solving [10], have demonstrated the feasibility of these retraining programs in either acquired or progressively deteriorating neurological conditions. Well-controlled, randomized larger scale investigations are needed for PD and other neurologically impaired population that take into account the specific disease characteristics of the population (e.g., duration of motor severity, medications), the specific cognitive domains affected in the population (e.g., executive dysfunction, visuospatial), the objective cognitive assessments, daily functioning assessments, and long-term outcome assessments.

Although the current studies in PD are limited in sample size, it appears that cognitive training programs are both feasible and well accepted by PD patients. The cognitive targets of the reviewed pilot studies focus on attention and executive impairments in nondemented patients using both computers and in-person interventions. As the literature

on cognitive rehabilitation programs grows, it would be beneficial for studies to use similar assessments to enhance comparisons between studies and to include both measures of neuropsychological and everyday functioning to evaluate the generalizability of the program into the patient's daily functioning. Based on the current literature, the effectiveness of cognitive training to demonstrate targeted short-term improvement on objective assessments following rehabilitation is promising [20–28]; however, long-term assessments of cognitive rehabilitation for patients with PD are needed. Both in-person and computerized training appear feasible but more information is needed on PD-related patient characteristics that predict success in cognitive rehabilitation interventions (e.g., age, length since diagnosis, type or severity of cognitive impairments). Executive dysfunction, which is an early indicator of PD-related cognitive decline and has a pervasive impact on daily functioning, has been identified as a target for cognitive rehabilitation in other populations. Accordingly, cognitive rehabilitation programs, particularly those that focus on improving executive functioning, have the potential to help patients with PD maintain a higher level of adaptive living skills and quality of life.

Future cognitive rehabilitation outcomes studies in PD will need to address the limitations uncovered in programs developed for other neurologically impaired populations and the obstacles inherent in working with PD patients. Cognitive rehabilitation is often time-consuming for patients, caregivers, and therapists and can be costly to implement. In addition to these logistical obstacles is the lack of ecologically valid outcome measures to demonstrate improvement in patients' daily functioning or generalization of their newly acquired abilities to other areas of daily living. Well-controlled and described randomized studies using appropriate control groups with longer-term follow-up evaluations including ecologically valid outcome measures would be an initial step to demonstrate actual efficacy of cognition rehabilitation in PD.

Additionally, PD itself poses several inherent obstacles for success in terms of cognitive rehabilitation. Researchers will also need to address these issues when developing future cognitive rehabilitation programs for patients with PD, including the heterogeneity of cognitive impairment, variability of functioning for patients with on/off fluctuations, cooccurring depression and anxiety, apathy, the mobility issues that restrict access to biweekly individualized programs, and the optimal disease stage in which improvements in cognitive functioning would be most beneficial. Personalized approaches to tailor treatment to individual strengths and deficits are recommended. If skills learned in cognitive rehabilitation carry over into everyday functioning and improve problem-solving and adaptive abilities, the programs could create positive and long-lasting benefits for patients by improving quality of life and potentially decreasing caregiver burden.

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